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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

a¹a²a³CDa⁶La⁸a⁹a¹⁰Ca¹²a¹³a¹⁴

(SEQ. ID. NO: 100),

b¹b²b³Cb⁵b⁶Db⁸Lb¹⁰b¹¹b¹²b¹³b¹⁴Cb¹⁶b¹⁷b¹⁸

(SEQ. ID. NO: 104)

c¹c²c³Cc⁵Dc⁷Lc⁹c¹⁰c¹¹c¹²c¹³c¹⁴Cc¹⁶c¹⁷c¹⁸

(SEQ. ID. NO: 105)

d¹d²d³Cd⁵d⁶d⁷WDd¹⁰Ld¹³d¹⁴d¹⁵Cd¹⁶d¹⁷d¹⁸

(SEQ. ID. NO: 106)

e¹e²e³Ce⁵e⁶e⁷De⁹Le¹¹Ke¹³Ce¹⁵e¹⁶e¹⁷e¹⁸

(SEQ. ID. NO: 107)

f¹f²f³Kf⁵Df⁷Lf⁹f¹⁰Qf¹²f¹³f¹⁴

(SEQ. ID. NO: 109)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz²Lz⁴ wherein z² is an amino acid residue and z⁴ is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae a¹a²a³CDa⁶La⁸a⁹a¹⁰Ca¹²a¹³a¹⁴ (SEQ.ID.NO:100), b¹b²b³Cb⁵b⁶Db⁸Lb¹⁰b¹¹b¹²b¹³b¹⁴Cb¹⁶b¹⁷b¹⁸ (SEQ.ID.NO:104) c¹c²c³Cc⁵Dc⁷Lc⁹c¹⁰c¹¹c¹²c¹³c¹⁴Cc¹⁶c¹⁷c¹⁸ (SEQ.ID.NO:105) d¹d²d³Cd⁵d⁶d⁷WDd¹⁰Ld¹³d¹⁴d¹⁵Cd¹⁶d¹⁷d¹⁸ (SEQ.ID.NO:106) e¹e²e³Ce⁵e⁶e⁷De⁹Le¹¹Ke¹³Ce¹⁵e¹⁶e¹⁷e¹⁸ (SEQ.ID.NO:107) f¹f²f³Kf⁵Df⁷Lf⁹f¹⁰Qf¹²f¹³f¹⁴ (SEQ.ID.NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula (X¹)_a-V¹-(X²)_b wherein V¹ is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.

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(X¹)_a-V¹-(X²)_b (I)



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PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196,
5 filed May 11, 2001, which is hereby incorporated by reference.

Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs) α and β were finally cloned in 1984. The ensuing years witnessed
10 the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith *et al.* (1994), *Cell* 76: 959-962;
15 Lacey *et al.* (1998), *Cell* 93: 165-176; Chicepotiche *et al.* (1997), *J. Biol. Chem.* 272: 32401-32410; Mauri *et al.* (1998), *Immunity* 8: 21-30; Hahne *et al.* (1998), *J. Exp. Med.* 188: 1185-90; Shu *et al.* (1999), *J. Leukocyte Biology* 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in
20 immune compartments, although some members are also expressed in other tissues or organs, as well. Smith *et al.* (1994), *Cell* 76: 959-62. All ligand members, with the exception of LT- α , are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity,
25 the conserved 150 amino acid domain folds into a characteristic β -pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner *et al.* (1993), *Cell* 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith *et al.* (1994). For example, TNF α is mainly synthesized by macrophages and is an important mediator for inflammatory responses and 5 immune defenses. Tracey & Cerami (1994), *Ann. Rev. Med.* 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) *Immunology Today* 16: 39-43; Castrim *et al.* (1996), *Immunity* 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and 10 immunoglobulin isotype switching. Noelle (1996), *Immunity* 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith *et al.* (1994). 15 The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF- κ B activation, or JNK activation. Wallach *et al.* (1999), *Annual Review of Immunology* 17: 331- 20 67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96: 3540-5.

25 A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokinin α (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,

published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare *et al.* (2000) *PNAS* 97(7):3370-3375. Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross *et al.* (2000), *Nature* 404: 995-999; Ware (2000), *J. Exp. Med.* 192(11): F35-F37; Ware (2000), *Nature* 404: 949-950; Xia *et al.* (2000), *J. Exp. Med.* 192(1):137-143; Yu *et al.* (2000), *Nature Immunology* 1(3):252-256; Marsters *et al.* (2000), *Current Biology* 10:785-788; Hatzoglou *et al.* (2000) *J. of Immunology* 165:1322-1330; Shu *et al.* (2000) *PNAS* 97(16):9156-9161; Thompson *et al.* (2000) *J. Exp. Med.* 192(1):129-135; Mukhopadhyay *et al.* (1999) *J. Biol. Chem.* 274(23): 15978-81; Shu *et al.* (1999) *J. Leukocyte Biol.* 65:680-683; Gruss *et al.* (1995) *Blood* 85(12): 3378-3404; Smith *et al.* (1994), *Cell* 76: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition, both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu *et al.* (2000), *Nature Immunology* 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent 5 application entitled, "Modified Peptides as Therapeutic Agents," published WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its 10 receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy.

Clackson *et al.* (1995), Science 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves 15 functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

20 Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott *et al.* (1990), Science 249: 386; Devlin *et al.* (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 25 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference in its entirety). In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify 5 key residues within one or more structurally related families of peptides. See, e.g., Cwirla *et al.* (1997), Science 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to 10 further optimize the sequence of the best binders. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity 15 and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki *et al.* (1997), Nature Biotech. 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the 20 peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor and expressed in E. coli. Another E. coli-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated 25 lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "E. coli display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phylos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any protein using phage display, RNA-peptide screening, and the other methods mentioned above.

Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz²Lz⁴ (SEQ ID NO: 108) wherein z² is an amino acid residue and z⁴ is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:

I(a) $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$
25 (SEQ. ID. NO: 100)

wherein:

a¹, a², a³ are each independently absent or amino acid residues;
a⁶ is an amino acid residue;
a⁹ is a basic or hydrophobic residue;
30 a⁸ is threonyl or isoleucyl;

a^{12} is a neutral polar residue; and

a^{13} and a^{14} are each independently absent or amino acid residues.

I(b)

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

5

(SEQ. ID. NO: 104)

wherein:

b^1 and b^2 are each independently absent or amino acid residues;

b^3 is an acidic or amide residue;

b^5 is an amino acid residue;

10

b^6 is an aromatic residue;

b^8 is an amino acid residue;

b^{10} is T or I;

b^{11} is a basic residue;

b^{12} and b^{13} are each independently amino acid residues;

15

b^{14} is a neutral polar residue; and

b^{16} , b^{17} , and b^{18} are each independently absent or amino acid residues.

I(c)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO:105)

20

wherein:

c^1 , c^2 , and c^3 are each independently absent or amino acid residues;

c^5 is an amino acid residue;

c^7 is an amino acid residue;

c^9 is T or I;

25

c^{10} is a basic residue;

c^{11} and c^{12} are each independently amino acid residues;

c^{13} is a neutral polar residue;

c^{14} is an amino acid residue;

c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and
 c^{18} is an amino acid residue or is absent.

I(d) $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{12}d^{13}d^{14}Cd^{15}d^{16}d^{17}$

(SEQ. ID. NO: 106)

5 wherein:

d^1 , d^2 , and d^3 are each independently absent or amino acid residues;

d^5 , d^6 , and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

d^{13} is T or I;

10 d^{14} is an amino acid residue; and

d^{16} , d^{17} , and d^{18} are each independently absent or amino acid residues.

I(e) $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

15 wherein:

e^1 , e^2 , and e^3 are each independently absent or amino acid residues;

e^5 , e^6 , e^7 , e^9 , and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15} , e^{16} , and e^{17} are each independently absent or amino acid residues.

20 I(f) $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

wherein:

f^1 , f^2 , and f^3 are absent or are amino acid residues (with one of f^1 , f^2 , and f^3 preferred to be C when one of f^{12} , f^{13} , and f^{14} is C);

25 f^5 is W, Y, or F (W preferred);

f^7 is an amino acid residue (L preferred);

f^9 is T or I (T preferred);

f^{10} is K, R, or H (K preferred);

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent (V preferred); and

5 f^{14} is any amino acid residue or is absent;

provided that only one of f^1 , f^2 , and f^3 may be C, and only one of f^{12} , f^{13} , and f^{14} may be C.

Compounds of formulae I(a) through I(f) above incorporate Dz^2Lz^4 , as well as SEQ ID NO: 63 hereinafter. The sequence of I(f) was derived as 10 a consensus sequence as described in Example 1 hereinbelow. Of compounds within formula I(f), those within the formula

I(f') $f^1f^2f^3KWDf^7Lf^8KQf^{12}f^{13}f^{14}$

(SEQ ID NO: 125)

are preferred. Compounds falling within formula I(f') include SEQ ID 15 NOS: 32, 58, 60, 62, 63, 66, 67, 69, 70, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, 187.

Also in accordance with the present invention are compounds having the consensus motif:

PFPWE

20 (SEQ ID NO: 110)

which also bind TALL-1.

Further in accordance with the present invention are compounds of the formulae:

I(g) $g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$

25 (SEQ. ID. NO. 101)

wherein:

g^1 , g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

30 g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and
 g^{14} is absent or is an amino acid residue.

I(h) $h^1h^2h^3CWh^6h^7W Gh^{10}Ch^{12}h^{13}h^{14}$

(SEQ. ID. NO: 102)

5 wherein:

h^1 , h^2 , and h^3 are each independently absent or amino acid residues;

h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;

h^{10} is an acidic or polar hydrophobic residue; and

10 h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues.

I(i) $i^{1,2}i^3Cii^{5,6,7,8,9}i^{10}C^{12,13}i^{14}$

(SEQ. ID. NO: 103)

wherein:

i^1 is absent or is an amino acid residue;

15 i^2 is a neutral polar residue;

i^3 is an amino acid residue;

i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;

i^9 is an acidic residue;

i^{10} is an amino acid residue;

20 i^{12} and i^{13} are each independently amino acid residues; and

i^{14} is a neutral polar residue.

The compounds defined by formulae I(g) through I(i) also bind

TALL-1.

Further in accordance with the present invention, modulators of

25 TALL-1 comprise:

a) a TALL-1 modulating domain (e.g., an amino acid sequence of Formulae I(a) through I(i)), preferably the amino acid sequence Dz^2Lz^4 , or sequences derived therefrom by phage display, RNA-peptide screening, or the other techniques mentioned above; and

30

b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred;

wherein the vehicle is covalently attached to the TALL-1 modulating domain. The vehicle and the TALL-1 modulating domain may be linked 5 through the N- or C-terminus of the TALL-1 modulating domain, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Such Fc-linked peptides are referred to herein as "peptibodies." Preferred TALL-1 modulating domains comprise the amino acid sequences described hereinafter in 10 Tables 1 and 2. Other TALL-1 modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein.

Further in accordance with the present invention is a process for making TALL-1 modulators, which comprises:

15 a. selecting at least one peptide that binds to TALL-1 ; and
b. covalently linking said peptide to a vehicle.

The preferred vehicle is an Fc domain. Step (a) is preferably carried out by selection from the peptide sequences in Table 2 hereinafter or from phage display, RNA-peptide screening, or the other techniques mentioned 20 herein.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins. Compounds of this invention that encompass non-peptide portions may be synthesized by standard organic 25 chemistry reactions, in addition to standard peptide chemistry reactions when applicable.

The primary use contemplated for the compounds of this invention is as therapeutic or prophylactic agents. The vehicle-linked peptide may

have activity comparable to—or even greater than—the natural ligand mimicked by the peptide.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate 5 pharmaceutical carrier materials and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the instant invention.

Numerous additional aspects and advantages of the present 10 invention will become apparent upon consideration of the figures and detailed description of the invention.

Brief Description of the Figures

Figure 1 shows exemplary Fc dimers that may be derived from an IgG1 antibody. "Fc" in the figure represents any of the Fc variants within the meaning of "Fc domain" herein. "X¹" and "X²" represent peptides or 15 linker-peptide combinations as defined hereinafter. The specific dimers are as follows:

A, D: Single disulfide-bonded dimers. IgG1 antibodies typically have two disulfide bonds at the hinge region of the antibody. The Fc 20 domain in Figures 1A and 1 D may be formed by truncation between the two disulfide bond sites or by substitution of a cysteinyl residue with an unreactive residue (e.g., alanyl). In Figure 1A, the Fc domain is linked at the amino terminus of the peptides; in 1D, at the carboxyl terminus.

B, E: Doubly disulfide-bonded dimers. This Fc domain may be formed by truncation of the parent antibody to retain both cysteinyl 25 residues in the Fc domain chains or by expression from a construct including a sequence encoding such an Fc domain. In Figure 1B, the Fc domain is linked at the amino terminus of the peptides; in 1E, at the carboxyl terminus.

C, F: Noncovalent dimers. This Fc domain may be formed by elimination of the cysteinyl residues by either truncation or substitution. One may desire to eliminate the cysteinyl residues to avoid impurities formed by reaction of the cysteinyl residue with cysteinyl residues of other 5 proteins present in the host cell. The noncovalent bonding of the Fc domains is sufficient to hold together the dimer. Other dimers may be formed by using Fc domains derived from different types of antibodies (e.g., IgG2, IgM).

Figure 2 shows the structure of preferred compounds of the 10 invention that feature tandem repeats of the pharmacologically active peptide. Figure 2A shows a single chain molecule and may also represent the DNA construct for the molecule. Figure 2B shows a dimer in which the linker-peptide portion is present on only one chain of the dimer. Figure 2C shows a dimer having the peptide portion on both chains. The dimer of 15 Figure 2C will form spontaneously in certain host cells upon expression of a DNA construct encoding the single chain shown in Figure 3A. In other host cells, the cells could be placed in conditions favoring formation of dimers or the dimers can be formed in vitro.

Figure 3 shows exemplary nucleic acid and amino acid sequences 20 (SEQ ID NOS: 1 and 2, respectively) of human IgG1 Fc that may be used in this invention.

Figures 4A through 4F show the nucleotide and amino acid sequences (SEQ ID NOS: 3-27) S of NdeI to SalI fragments encoding peptide and linker.

25 Figures 5A through 5M show the nucleotide sequence (SEQ ID NO: 28) of pAMG21-RANK-Fc vector, which was used to construct Fc-linked molecules of the present invention. These figures identify a number of features of the nucleic acid, including:

- promoter regions PcopB, PrepA, RNAI, APHII, luxPR, and luxPL;
- 30 • mRNA for APHII, luxR;

- coding sequences and amino acid sequences for the proteins copB protein, copT, repAI, repA4, APHII, luxR, RANK, and Fc;
- binding sites for the proteins copB, CRP;
- hairpins T1, T2, T7, and toop;
- 5 • operator site for lux protein;
- enzyme restriction sites for PflIl08I, BglII, ScaI, BmnI, DrdII, DraIII, BstBI, AceIII, AflII, PflMI, BglII, SfiI, BstEII, BspLullI, NspV, BplI, EagI, BcgI, NsiI, BsaI, PspI406I, AatII, BsmI, NruI, NdeI, ApaLI, Acc65I, KpnI, SalI, AccI, BspEI, AhdI, BspHI, EcoNI, BsrGI, BmaI, SmaI, SexAI, BamHI, and BplI.

10 Figures 6A and 6B show the DNA sequence (SEQ ID NO: 97) inserted into pCFM1656 between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites to form expression plasmid pAMG21 (ATCC accession no. 98113).

15 Figure 7 shows that the TALL-1 peptibody (SEQ ID NO: 70) inhibits TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 consensus peptibody in the presence of 10 ng/ml TALL-1 plus 2 μ g/ml anti-IgM antibody. Proliferation was measured by radioactive [3 H]thymidine uptake in the last 18h of pulse. Data shown represent mean \pm SD triplicate wells.

20 Figure 8 shows that a TALL-1 N-terminal tandem dimer peptibodies (SEQ ID NO: 123, 124 in Table 5B hereinafter) are preferable for inhibition of TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 12-3 peptibody and TALL-1 consensus peptibody (SEQ ID NOS: 115 and 122 of Table 5B) or the related dimer peptibodies (SEQ ID NOS: 123, 124) in the presence of 10 ng/ml TALL-1 plus 2 μ g/ml anti-IgM antibody. Proliferation was measured by radioactive [3 H]thymidine uptake in the last 18h of pulse. Data shown represent mean \pm SD triplicate wells.

25 Figure 9. AGP3 peptibody binds to AGP3 with high affinity.
30 Dissociation equilibrium constant (K_D) was obtained from nonlinear regression

of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody binding with human AGP3 (SEQ ID NO: 123).

Figures 10A and 10B. AGP3 peptibody blocks both human and murine AGP3 in the Biacore competition assay. Soluble human TACI protein was immobilized to B1 chip. 1 nM of recombinant human AGP3 protein (upper panel) or 5 nM of recombinant murine AGP3 protein (lower panel) was incubated with indicated amount of AGP3 peptibody before injected over the surface of receptor. Relative human AGP3 and murine AGP3 (binding response was shown (SEQ ID NO: 123)).

Figures 11A and 11B. AGP3 peptibody blocked AGP3 binding to all three receptors TACI, BCMA and BAFFR in Biacore competition assay. Recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. 1 nM of recombinant human AGP3 (upper panel) were incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. Relative binding of AGP3 was measured. Similarly, 1 nM of recombinant APRIL protein was incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. AGP3 peptibody didn't inhibit APRIL binding to all three receptors (SEQ ID NO: 123).

Figures 12A and 12B. AGP3 peptibody inhibits mouse serum immunoglobulin level increase induced by human AGP3 challenge. Balb/c mice received 7 daily intraperitoneal injections of 1 mg/Kg human AGP3 protein along with saline, human Fc, or AGP3 peptibody at indicated doses, and were bled on day 8. Serum total IgM and IgA level were measured by ELISA (SEQ ID NO: 123).

Figure 13. AGP3 peptibody treatment reduced arthritis severity in the mouse CIA model. Eight to 12 weeks old DBA/1 male mice were immunized with bovine collagen type II (bCII) emulsified in complete freunds adjuvant intradermally at the base of tail, and were boosted 3 weeks after the initial immunization with bCII emulsified in incomplete freunds adjuvant. Treatment with indicated dosage of AGP3 peptibody was begun from the day of booster

immunization for 4 weeks. As described before (Khare et al., *J. Immunol.*.. 155: 3653-9, 1995), all four paws were individually scored from 0-3 for arthritis severity (SEQ ID NO: 123).

Figure 14. AGP3 peptibody treatment inhibited anti-collagen antibody 5 generation in the mouse CIA model. Serum samples were taken one week after final treatment (day 35) as described above. Serum anti-collagen II antibody level was determined by ELISA analysis (SEQ ID NO: 123).

Figures 15A and 15B. AGP3 peptibody treatment delayed proteinuria onset and improved survival in NZB/NZW lupus mice. Five-month-old lupus 10 prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody (SEQ ID NO: 123) or human Fc proteins. Protein in the urine was evaluated monthly throughout the life of the experiment with Albustix reagent strips (Bayer AG).

Figures 16A and 16B show the nucleic acid and amino acid 15 sequences of a preferred TALL-1-binding peptibody (SEQ ID NOS: 189 and 123)

Detailed Description of the Invention

Definition of Terms

20 The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

General definitions

The term "comprising" means that a compound may include 25 additional amino acids on either or both of the N- or C- termini of the given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound.

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. The term "physiologically acceptable salts" refers to any salts that are known or later discovered to 30 be pharmaceutically acceptable. Some specific examples are: acetate;

trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; tartrate; glycolate; and oxalate.

Amino acids

The term "acidic residue" refers to amino acid residues in D- or L-
5 form having sidechains comprising acidic groups. Exemplary acidic residues include D and E.

The term "amide residue" refers to amino acids in D- or L-form having sidechains comprising amide derivatives of acidic groups. Exemplary residues include N and Q.

10 The term "aromatic residue" refers to amino acid residues in D- or L-form having sidechains comprising aromatic groups. Exemplary aromatic residues include F, Y, and W.

15 The term "basic residue" refers to amino acid residues in D- or L-form having sidechains comprising basic groups. Exemplary basic residues include H, K, and R.

The term "hydrophilic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary hydrophilic residues include C, S, T, N, and Q.

20 The term "nonfunctional residue" refers to amino acid residues in D- or L-form having sidechains that lack acidic, basic, or aromatic groups. Exemplary nonfunctional amino acid residues include M, G, A, V, I, L and norleucine (Nle).

The term "neutral polar residue" refers to amino acid residues in D- or L-form having sidechains that lack basic, acidic, or polar groups.

25 Exemplary neutral polar amino acid residues include A, V, L, I, P, W, M, and F.

The term "polar hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary polar hydrophobic amino acid residues include T, G, S, Y, C, Q, and N.

The term "hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains that lack basic or acidic groups. Exemplary hydrophobic amino acid residues include A, V, L, I, P, W, M, F, T, G, S, Y, C, Q, and N.

5 Peptides

The term "peptide" refers to molecules of 1 to 40 amino acids, with molecules of 5 to 20 amino acids preferred. Exemplary peptides may comprise the TALL-1 modulating domain of a naturally occurring molecule or comprise randomized sequences.

10 The term "randomized" as used to refer to peptide sequences refers to fully random sequences (e.g., selected by phage display methods or RNA-peptide screening) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary
15 methods for identifying peptide sequences include phage display, E. coli display, ribosome display, RNA-peptide screening, chemical screening, and the like.

20 The term "TALL-1 modulating domain" refers to any amino acid sequence that binds to the TALL-1 and comprises naturally occurring sequences or randomized sequences. Exemplary TALL-1 modulating domains can be identified or derived by phage display or other methods mentioned herein.

25 The term "TALL-1 antagonist" refers to a molecule that binds to the TALL-1 and increases or decreases one or more assay parameters opposite from the effect on those parameters by full length native TALL-1. Such activity can be determined, for example, by such assays as described in the subsection entitled "Biological activity of AGP-3" in the Materials & Methods section of the patent application entitled, "TNF-RELATED PROTEINS", WO 00/47740, published August 17, 2000.

Vehicles and peptibodies

The term "vehicle" refers to a molecule that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein. Exemplary vehicles include an Fc domain (which is preferred) as well as a linear polymer (e.g., polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain polymer (see, for example, U.S. Patent No. 4,289,872 to Denkenwalter et al., issued September 15, 1981; 5,229,490 to Tam, issued July 20, 1993; WO 93/21259 by Frechet et al., published 28 October 1993); a lipid; a cholesterol group (such as a steroid); a carbohydrate or oligosaccharide (e.g., dextran); any natural or synthetic protein, polypeptide or peptide that binds to a salvage receptor; albumin, including human serum albumin (HSA), leucine zipper domain, and other such proteins and protein fragments. Vehicles are further described hereinafter.

The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. The original immunoglobulin source of the native Fc is preferably of human origin and may be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Native Fc's are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al.

(1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference in their entirety. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means.

The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers,

trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Thus, exemplary dimers within the scope of this invention are as shown in Figure 1.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or *in vivo*; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by -NRR¹, NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R¹ and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by -C(O)R² or -NR³R⁴ wherein R², R³ and R⁴ are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

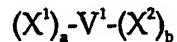
The terms "peptibody" and "peptibodies" refer to molecules comprising an Fc domain and at least one peptide. Such peptibodies may be multimers or dimers or fragments thereof, and they may be derivatized. In the present invention, the molecules of formulae II through VI hereinafter are peptibodies when V¹ is an Fc domain.

Structure of compounds

In General. The present inventors identified sequences capable of binding to and modulating the biological activity of TALL-1. These sequences can be modified through the techniques mentioned above 5 by which one or more amino acids may be changed while maintaining or even improving the binding affinity of the peptide.

In the compositions of matter prepared in accordance with this invention, the peptide(s) may be attached to the vehicle through the peptide's N-terminus or C-terminus. Any of these peptides may be linked 10 in tandem (i.e., sequentially), with or without linkers. Thus, the vehicle-peptide molecules of this invention may be described by the following formula:

II



15 wherein:

V^1 is a vehicle (preferably an Fc domain);

X^1 and X^2 are each independently selected from $-(L^1)_c \cdot P^1$, $-(L^1)_c \cdot P^1 \cdot (L^2)_d \cdot P^2$, $-(L^1)_c \cdot P^1 \cdot (L^2)_d \cdot P^2 \cdot (L^3)_e \cdot P^3$, and $-(L^1)_c \cdot P^1 \cdot (L^2)_d \cdot P^2 \cdot (L^3)_e \cdot P^3 \cdot (L^4)_f \cdot P^4$

P^1 , P^2 , P^3 , and P^4 are each independently sequences of TALL-1

20 modulating domains, such as those of Formulae I(a) through I(i);

L^1 , L^2 , L^3 , and L^4 are each independently linkers; and

a , b , c , d , e , and f are each independently 0 or 1, provided that at least one of a and b is 1.

Thus, compound II comprises preferred compounds of the 25 formulae

III



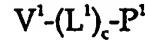
and multimers thereof wherein V^1 is an Fc domain and is attached at the C-terminus of A^1 ;

IV



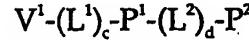
and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of A^2 ;

5 V



and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $-(L^1)_c-P^1$; and

VI



and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $-L^1-P^1-L^2-P^2$.

10 Peptides. The peptides of this invention are useful as TALL-1 modulating peptides or as TALL-1 modulating domains in the molecules
15 of formulae II through VI. Molecules of this invention comprising these peptide sequences may be prepared by methods known in the art.

Preferred peptide sequences are those of the foregoing formulae I(a) having the substituents identified below.

Table 1--Preferred peptide substituents

| | |
|--------------|--|
| Formula I(a) | a^8 is T; a^9 is a basic residue (K most preferred); and a^{12} is a neutral polar residue (F most preferred). |
| Formula I(b) | b^3 is D, Q, or E; b^6 is W or Y; b^{10} is T; b^{11} is K or R; and b^{14} is V or L. |
| Formula I(c) | c^9 is T; c^{10} is K or R; c^{13} is a I, L, or V; and c^{17} is A or L. |
| Formula I(d) | d^{13} is T. |
| Formula I(e) | e^{11} is T. |
| Formula I(f) | f^6 is T; f^7 is K; and f^{10} is V. |
| Formula I(g) | g^5 is W; g^8 is P; g^{10} is E; and g^{13} is a basic residue. |
| Formula I(h) | h^1 is G; h^6 is A; h^7 is a neutral polar residue; and h^{10} is an acidic residue. |
| Formula I(i) | i^2 is W; and i^{14} is W. |

Preferred peptide sequences appear in Table 2 below.

Table 2—Preferred TALL-1 modulating domains

| Sequence | SEQ ID NO: |
|----------------------|------------|
| PGTCFPFPWECTHA | 29 |
| WGACWPFPWECFKE | 30 |
| VPFCDLLTKHCFEA | 31 |
| GSRCKYKWDVLTQCFHH | 32 |
| LPGCKWDLLIKQWVCDPL | 33 |
| SADCYFDILTKSDVCTSS | 34 |
| SDDCMYDQLTRMFICSNL | 35 |
| DLNCKYDELTYKEWCQFN | 36 |
| FHDCKYDLLTRQMVCHGL | 37 |
| RNHCFWDHLLKQDICPSP | 38 |
| ANQCWWDSLTKKNVCEFF | 39 |
| YKGRCQWDILTRSWVVS | 126 |
| QDVGLWWWDILTRAWSMPNI | 127 |
| QNAQRVWDLLIRTWVYPO | 128 |
| GWNEAWWDELTKIWWLLEQ | 129 |
| RITCDTWDSLLIKCKVCPQS | 130 |
| GAIMQFWDSLTKTWRQSQ | 131 |
| WLHSGWWWDPLTKHWLQKV | 132 |
| SEWFFWFDPPLTRAQLKFR | 133 |
| GVWFWWFDPLTKQWTQAG | 134 |
| MQCKGYYDILTKWCVTNG | 135 |
| LWSKEVWDILTKSWVSQA | 136 |
| KAAGWWFDWLTKVWVPAP | 137 |
| AYQTFWFWDLSITRLWLSTT | 138 |
| SGQHFWWDLLTRSWTPST | 139 |
| LGVGQKWDPLTKQWVSRG | 140 |
| VGKMCQWDPLIKRTVCVG | 141 |
| CRQGAKFDLLTKQCLLGR | 142 |
| GQAIRHWDVLTQWVDSQ | 143 |
| RGPGCSWDLLTKHCLDSQ | 144 |
| WQWKQQWDLLTKQMVWVG | 145 |
| PITICRKDLLTKQVVCLD | 146 |
| KTCNGKWDLLTKQCLQQA | 147 |
| KCLKGKWDLLTKQCVTEV | 148 |
| RCWNGKWDLLTKQCIHPW | 149 |
| NRDMRKWDPLIKQWIVRP | 150 |
| QAAAATWDLLTKQWLVP | 151 |
| PEGGPKWDPLTKQFLPPV | 152 |
| QTPQKKWDLLTKQWFTRN | 153 |
| IGSPCKWDLLTKQMICQT | 154 |
| CTAAGKWDLLTKQCIQEK | 155 |
| VSQCMKWDLLTKQCLQGW | 156 |
| VWGTWKWDLLTKQYLPPQ | 157 |
| GWEMKWDLLTKQWYRPQ | 158 |
| TAQVSKWDLLTKQWLPLA | 159 |
| QLWGTWKWDLLTKQYIQIM | 160 |
| WATSQKWDLLTKQWVQNM | 161 |
| ORQCAKWDLLTKQCVLFY | 162 |

| | |
|---------------------|-----|
| KTTDCWKDLLTKQRICQV | 163 |
| LLCQGKWDLLTKQCLKLR | 164 |
| LMWFWKWDLLTKQLVPTF | 165 |
| QTWAWKWDLLTKQWIGPM | 166 |
| NKELLKWDLLTKQCRGRS | 167 |
| GQKDLKWDLLTKQYVRQS | 168 |
| PKPCQKWDLLTKQCLGSV | 169 |
| GOIGWKWDLLTKQWIQTR | 170 |
| VWLDWKWDLLTKQWIHPQ | 171 |
| QEWEYKWDLLTKQWGWLRL | 172 |
| HWDWKWDLLTKQWVVQA | 173 |
| TRPLQKWDLLTKQWLVRG | 174 |
| SDQWQKWDLLTKQWFWDV | 175 |
| QQTFMKWDLLTKQWIRRH | 176 |
| QGECRKWDLLTKQCFPGQ | 177 |
| GQMGWRWDPLIKMCLGPS | 178 |
| QLDGCKWDLLTKQKVCP | 179 |
| HGYWQKWDLLTKQWVSSE | 180 |
| HQGQCGWDLLTRIYLPCH | 181 |
| LHKACKWDLLTKQCWPMQ | 182 |
| GPPGSVWDLLTKIWIQTG | 183 |
| ITQDWRFDTLTRLWLPLR | 184 |
| QGGFAAWDVLTkmWITVP | 185 |
| GHGTPWWDALTRIWILGV | 186 |
| VWPWQKWDLLTKQFVFQD | 187 |
| WQWSWKWDLLTRQYISSS | 188 |
| NOTLWKWDLLTKQFITYM | 60 |
| PVYQGWWDTLTKLYIWDG | 61 |
| WLDGGWRDPLIKRSVQLG | 62 |
| GHQQFKWDLLTKQWVQSN | 63 |
| ORVGQFWDVLTkmFITGS | 64 |
| QAQGWSYDALIKTWIRWP | 65 |
| GMWHRWKWDPLTKQALPWM | 66 |
| GHPTYKWDLLTKQWILQM | 67 |
| WNNWSLWDPLTKLWLQON | 68 |
| WQWGWKWDLLTKQWVQOO | 69 |
| GQMGWRWDPLTKMWLGTS | 70 |

It is noted that the known receptors for TALL-1 bear some sequence homology with preferred peptides:

12-3 LPGCKWDLLIKQWVCDPL
5 BAFFR MRRGPRSLRGRDAPVPTPCVPTECYDLLVRKCVDCRLL
TACI TICNHQSORTCAAFCRSLSCRKEQGKFYDHLLRDCISCAPI
BCMA FVSPSQEIRGRFRRMLQMAGQCSQNEYFDSLHACIPCQLRC
(SEQ ID NOS: 33, 195, 196, and 197, respectively).

Any peptide containing a cysteiny1 residue may be cross-linked with
10 another Cys-containing peptide, either or both of which may be linked to a

vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized as described hereinafter.

Additional useful peptide sequences may result from conservative 5 and/or non-conservative modifications of the amino acid sequences of the sequences in Table 2.

Conservative modifications will produce peptides having functional and chemical characteristics similar to those of the peptide from which such modifications are made. In contrast, substantial modifications 10 in the functional and/or chemical characteristics of the peptides may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule 15 at the target site, or (c) the size of the molecule.

For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the 20 polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis" (see, for example, MacLennan *et al.*, 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki *et al.*, 1998, Adv. Biophys. 35:1-24, which discuss alanine scanning mutagenesis).

Desired amino acid substitutions (whether conservative or non- 25 conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the peptide sequence, or to increase or decrease the affinity of the peptide or vehicle-peptide molecules (see preceding formulae) described herein. Exemplary amino acid 30 substitutions are set forth in Table 3.

Table 3—Amino Acid Substitutions

| Original Residues | Exemplary Substitutions | Preferred Substitutions |
|-------------------|---|-------------------------|
| Ala (A) | Val, Leu, Ile | Val |
| Arg (R) | Lys, Gln, Asn | Lys |
| Asn (N) | Gln | Gln |
| Asp (D) | Glu | Glu |
| Cys (C) | Ser, Ala | Ser |
| Gln (Q) | Asn | Asn |
| Glu (E) | Asp | Asp |
| Gly (G) | Pro, Ala | Ala |
| His (H) | Asn, Gln, Lys, Arg | Arg |
| Ile (I) | Leu, Val, Met, Ala, Phe, Norleucine | Leu |
| Leu (L) | Norleucine, Ile, Val, Met, Ala, Phe | Ile |
| Lys (K) | Arg, 1,4 Diamino-butyric Acid, Gln, Asn | Arg |
| Met (M) | Leu, Phe, Ile | Leu |
| Phe (F) | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro (P) | Ala | Gly |
| Ser (S) | Thr, Ala, Cys | Thr |
| Thr (T) | Ser | Ser |
| Trp (W) | Tyr, Phe | Tyr |
| Tyr (Y) | Trp, Phe, Thr, Ser | Phe |
| Val (V) | Ile, Met, Leu, Phe, Ala, Norleucine | Leu |

5 In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are

typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

As noted in the foregoing section "Definition of Terms," naturally occurring residues may be divided into classes based on common sidechain properties that may be useful for modifications of sequence. For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into regions of the peptide that are homologous with non-human orthologs, or into the non-homologous regions of the molecule. In addition, one may also make modifications using P or G for the purpose of influencing chain orientation.

In making such modifications, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics, these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte *et al.*, *J. Mol. Biol.*, 157: 105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its 5 immunogenicity and antigenicity, *i.e.*, with a biological property of the protein.

The following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); 10 threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those which are within ±1 15 are particularly preferred, and those within ±0.5 are even more particularly preferred. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

A skilled artisan will be able to determine suitable variants of the 20 polypeptide as set forth in the foregoing sequences using well known techniques. For identifying suitable areas of the molecule that may be changed without destroying activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other 25 species are known, one skilled in the art may compare the amino acid sequence of a peptide to similar peptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of a peptide that are not conserved relative to such similar peptides would

be less likely to adversely affect the biological activity and/or structure of the peptide. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity (conservative 5 amino acid residue substitutions). Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the peptide structure.

Additionally, one skilled in the art can review structure-function 10 studies identifying residues in similar peptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a peptide that correspond to amino acid residues that are important for activity or structure in similar peptides. One skilled in the art may opt for chemically similar amino acid 15 substitutions for such predicted important amino acid residues of the peptides.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of that information, one skilled in the art may 20 predict the alignment of amino acid residues of a peptide with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may 25 generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such data could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed,

undesirably reduced, or unsuitable activity, variants with such a change would be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or 5 in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4): 422-427 (1996), Chou et al., Biochemistry, 13(2): 222-245 (1974); Chou et al., Biochemistry, 113(2): 211-222 (1974); Chou et al., Adv. Enzymol. Relat. 10 Areas Mol. Biol., 47: 45-148 (1978); Chou et al., Ann. Rev. Biochem., 47: 251-276 and Chou et al., Biophys. J., 26: 367-384 (1979). Moreover, computer programs are currently available to assist with predicting 15 secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural data base (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., Nucl. 20 Acid. Res., 27(1): 244-247 (1999). It has been suggested (Brenner et al., Curr. Op. Struct. Biol., 7(3): 369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will gain dramatically in accuracy.

25 Additional methods of predicting secondary structure include "threading" (Jones, D., Curr. Opin. Struct. Biol., 7(3): 377-87 (1997); Sippl et al., Structure, 4(1): 15-9 (1996)), "profile analysis" (Bowie et al., Science, 253: 164-170 (1991); Gribskov et al., Meth. Enzym., 183: 146-159 (1990);

Gribskov *et al.*, Proc. Nat. Acad. Sci., 84(13): 4355-8 (1987)), and "evolutionary linkage" (See Home, supra, and Brenner, supra).

Vehicles. This invention requires the presence of at least one vehicle (V¹) attached to a peptide through the N-terminus, C-terminus or a 5 sidechain of one of the amino acid residues. Multiple vehicles may also be used; e.g., Fc's at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain. Exemplary vehicles include:

- an Fc domain;
- other proteins, polypeptides, or peptides capable of binding to a 10 salvage receptor;
- human serum albumin (HSA);
- a leucine zipper (LZ) domain;
- polyethylene glycol (PEG), including 5 kD, 20 kD, and 30 kD PEG, as well as other polymers;
- dextran;

15 and other molecules known in the art to provide extended half-life and/or protection from proteolytic degradation or clearance.

An Fc domain is the preferred vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini. 20 Fusion to the N terminus is preferred.

As noted above, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478. 25 In such Fc variants, one may remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted

residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

- 5 1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other 10 amino acids (e.g., alanyl, seryl). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 2 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 2. Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.
- 15 2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in *E. coli* such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is 20 expressed recombinantly in a bacterial cell such as *E. coli*. The Fc domain of SEQ ID NO: 2 is one such Fc variant.
- 25 3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).

5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.
6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.
- 10 7. The ADCC site is removed. ADCC sites are known in the art; see, for example, *Molec. Immunol.* 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
- 15 8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In SEQ ID NO: 2 (Figure 3), the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenylalanine residues.

An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta *et al.* Peptides could also be selected by phage display or RNA-peptide screening for binding to the

FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased

5 immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

As noted above, polymer vehicles may also be used for V¹. Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

15 A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kD, more preferably from about 5 kD to about 50 kD, most preferably from about 5 kD to about 10 kD. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

20 25 A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis. The peptides are "preactivated" with

an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated 5 peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextrans are polysaccharide 10 polymers comprised of individual subunits of glucose predominantly linked by α 1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another 15 vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference in its entirety. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a 20 vehicle in accordance with the present invention.

Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in preferred embodiments, the linker is made up of from 1 to 30 25 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. In a more preferred embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably,

a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers are polyglycines (particularly (Gly)₄, (Gly)₅), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

5 (Gly)₃Lys(Gly)₄ (SEQ ID NO: 40);
 (Gly)₃AsnGlySer(Gly)₂ (SEQ ID NO: 41);
 (Gly)₃Cys(Gly)₄ (SEQ ID NO: 42); and
 GlyProAsnGlyGly (SEQ ID NO: 43).

To explain the above nomenclature, for example, (Gly)₃Lys(Gly)₄ means 10 Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly (SEQ ID NO: 40). Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

Preferred linkers are amino acid linkers comprising greater than 5 15 amino acids, with suitable linkers having up to about 500 amino acids selected from glycine, alanine, proline, asparagine, glutamine, lysine, threonine, serine or aspartate. Linkers of about 20 to 50 amino acids are most preferred. One group of preferred linkers are those of the formulae



20 (SEQ ID NO: 193)

and



(SEQ ID NO: 194)

wherein x¹ and x³ are each independently basic or hydrophobic residues 25 and x² and x⁴ are each independently hydrophobic residues. Specific preferred linkers are:



(SEQ ID NO: 59)

GSGSATGGSGSTASSGSGSATGM

(SEQ ID NO: 190)

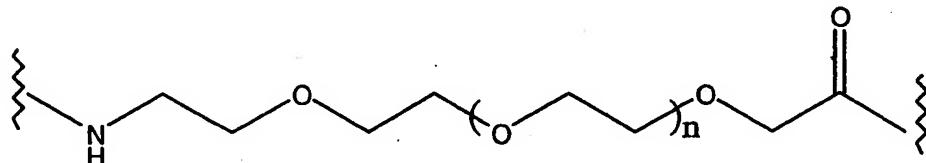
GSGSATGGSGSTASSGSGSATGS

(SEQ ID NO: 191), and

5 GSGSATGGSGTASSGSGSATMGSATGGSGTASSGSGSATM
(SEQ ID NO: 192).

Non-peptide linkers are also possible. For example, alkyl linkers such as $-\text{NH}-(\text{CH}_2)_s-\text{C}(\text{O})-$, wherein $s = 2-20$ could be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2 , phenyl, etc. An exemplary non-peptide linker is a PEG linker,

vii



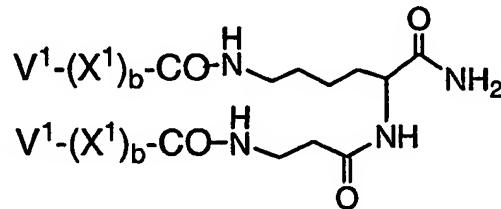
15 wherein n is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The inventors also contemplate derivatizing the peptide and/or vehicle portion of the compounds. Such derivatives may improve the solubility, absorption, biological half life, and the like of the compounds. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

25 1. The compound or some portion thereof is cyclic. For example, the peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound 5 may also be cross-linked through its C-terminus, as in the molecule shown below.

VIII



In Formula VIII, each "V¹" may represent typically one strand of the Fc 10 domain.

3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH₂- carbamate [-CH₂-OC(O)NR-], phosphonate, -CH₂-sulfonamide [-CH₂-S(O)₂NR-], urea [-NHC(O)NH-], -CH₂-secondary amine, and alkylated 15 peptide [-C(O)NR⁶- wherein R⁶ is lower alkyl].

4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR¹ (other than -NH₂), -NRC(O)R¹, -NRC(O)OR¹, -NRS(O)₂R¹, -NHC(O)NHR¹, succinimide, or 20 benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R¹ are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, chloro, and bromo.

5. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. Exemplary C-terminal derivative groups 25 include, for example, -C(O)R² wherein R² is lower alkoxy or -NR³R⁴

wherein R³ and R⁴ are independently hydrogen or C₁-C₈ alkyl (preferably C₁-C₄ alkyl).

6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar *et al.*

5 (1996), *J. Med. Chem.* 39: 3814-9; Alberts *et al.* (1993) *Thirteenth Am. Pep. Symp.*, 357-9.

7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.

10 Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction 15 with glyoxylate.

20 Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

25 Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl sidechain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides ($R'-N=C=N-R'$) such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues 5 may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues 10 falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar *et al.* (1996), *J. Med. Chem.* 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the 15 peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'- 20 dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming cross-links in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates 25 and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins.

Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably 5 one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer 10 acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, 15 COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino 20 groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be 25 changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected

host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

Methods of Making

The compounds of this invention largely may be made in 5 transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be 10 synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule 15 that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals, 20 cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

25 Any of a large number of available and well-known host cells may be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of

transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines,

5 useful microbial hosts include bacteria (such as E. coli sp.), yeast (such as Saccharomyces sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

Next, the transformed host is cultured and purified. Host cells may be cultured under conventional fermentation conditions so that the

10 desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable

15 techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins 20 (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

Compounds that contain derivatized peptides or which contain

25 non-peptide groups may be synthesized by well-known organic chemistry techniques.

Uses of the Compounds

Compounds of this invention may be particularly useful in treatment of B-cell mediated autoimmune diseases. In particular, the

compounds of this invention may be useful in treating, preventing, ameliorating, diagnosing or prognosing lupus, including systemic lupus erythematosus (SLE), and lupus-associated diseases and conditions. Other preferred indications include B-cell mediated cancers, including B-cell lymphoma.

5 The compounds of this invention can also be used to treat inflammatory conditions of the joints. Inflammatory conditions of a joint are chronic joint diseases that afflict and disable, to varying degrees, millions of people worldwide. Rheumatoid arthritis is a disease of 10 articular joints in which the cartilage and bone are slowly eroded away by a proliferative, invasive connective tissue called pannus, which is derived from the synovial membrane. The disease may involve peri-articular structures such as bursae, tendon sheaths and tendons as well as extra-articular tissues such as the subcutis, cardiovascular system, lungs, spleen, 15 lymph nodes, skeletal muscles, nervous system (central and peripheral) and eyes (Silberberg (1985), Anderson's Pathology, Kissane (ed.), II:1828). Osteoarthritis is a common joint disease characterized by degenerative changes in articular cartilage and reactive proliferation of bone and cartilage around the joint. Osteoarthritis is a cell-mediated active process 20 that may result from the inappropriate response of chondrocytes to catabolic and anabolic stimuli. Changes in some matrix molecules of articular cartilage reportedly occur in early osteoarthritis (Thonar *et al.* (1993), Rheumatic disease clinics of North America, Moskowitz (ed.), 19:635-657 and Shinmei *et al.* (1992), *Arthritis Rheum.*, 35:1304-1308). 25 TALL-1, TALL-1R and modulators thereof are believed to be useful in the treatment of these and related conditions.

Compounds of this invention may also be useful in treatment of a number of additional diseases and disorders, including:

- acute pancreatitis;

- ALS;
- Alzheimer's disease;
- asthma;
- atherosclerosis;
- 5 • autoimmune hemolytic anemia;
- cancer, particularly cancers related to B cells;
- cachexia/anorexia;
- chronic fatigue syndrome;
- cirrhosis (e.g., primary biliary cirrhosis);
- 10 • diabetes (e.g., insulin diabetes);
- fever;
- glomerulonephritis, including IgA glomerulonephritis and primary glomerulonephritis;
- Goodpasture's syndrome;
- 15 • Guillain-Barre syndrome;
- graft versus host disease;
- Hashimoto's thyroiditis;
- hemorrhagic shock;
- hyperalgesia;
- 20 • inflammatory bowel disease;
- inflammatory conditions of a joint, including osteoarthritis, psoriatic arthritis and rheumatoid arthritis;
- inflammatory conditions resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes;
- 25 • insulin-dependent diabetes mellitus;

- ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration);
- learning impairment;
- 5 • lung diseases (e.g., ARDS);
- multiple myeloma;
- multiple sclerosis;
- Myasthenia gravis;
- myelogenous (e.g., AML and CML) and other leukemias;
- 10 • myopathies (e.g., muscle protein metabolism, esp. in sepsis);
- neurotoxicity (e.g., as induced by HIV);
- osteoporosis;
- pain;
- Parkinson's disease;
- 15 • Pemphigus;
- polymyositis/dermatomyositis;
- pulmonary inflammation, including autoimmune pulmonary inflammation;
- pre-term labor;
- 20 • psoriasis;
- Reiter's disease;
- reperfusion injury;
- septic shock;
- side effects from radiation therapy;
- 25 • Sjogren's syndrome;
- sleep disturbance;
- temporal mandibular joint disease;

- thrombocytopenia, including idiopathic thrombocytopenia and autoimmune neonatal thrombocytopenia;
- tumor metastasis;
- uveitis; and
- vasculitis.

5

Compounds of this invention may be administered alone or in combination with a therapeutically effective amount of other drugs, including analgesic agents, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and any 10 immune and/or inflammatory modulators. Thus, compounds of this invention may be administered with:

- Modulators of other members of the TNF/TNF receptor family, including TNF antagonists, such as etanercept (Enbrel™), sTNF-RI, onercept, D2E7, and Remicade™.
- Nerve growth factor (NGF) modulators.
- IL-1 inhibitors, including IL-1ra molecules such as anakinra and more recently discovered IL-1ra-like molecules such as IL-1Hy1 and IL-1Hy2; IL-1 "trap" molecules as described in U.S. Pat. No. 5,844,099, issued December 1, 1998; IL-1 antibodies; solubilized 20 IL-1 receptor, and the like.
- IL-6 inhibitors (e.g., antibodies to IL-6).
- IL-8 inhibitors (e.g., antibodies to IL-8).
- IL-18 inhibitors (e.g., IL-18 binding protein, solubilized IL-18 receptor, or IL-18 antibodies).
- Interleukin-1 converting enzyme (ICE) modulators.
- insulin-like growth factors (IGF-1, IGF-2) and modulators thereof.
- Transforming growth factor- β (TGF- β), TGF- β family members, and TGF- β modulators.

25

- Fibroblast growth factors FGF-1 to FGF-10, and FGF modulators.
- Osteoprotegerin (OPG), OPG analogues, osteoprotective agents, and antibodies to OPG-ligand (OPG-L).
- 5 • bone anabolic agents, such as parathyroid hormone (PTH), PTH fragments, and molecules incorporating PTH fragments (e.g., PTH (1-34)-Fc).
- PAF antagonists.
- Keratinocyte growth factor (KGF), KGF-related molecules (e.g., KGF-2), and KGF modulators.
- 10 • COX-2 inhibitors, such as Celebrex™ and Vioxx™.
- Prostaglandin analogs (e.g., E series prostaglandins).
- Matrix metalloproteinase (MMP) modulators.
- Nitric oxide synthase (NOS) modulators, including modulators of inducible NOS.
- 15 • Modulators of glucocorticoid receptor.
- Modulators of glutamate receptor.
- Modulators of lipopolysaccharide (LPS) levels.
- Anti-cancer agents, including inhibitors of oncogenes (e.g., fos, jun) and interferons.
- 20 • Noradrenaline and modulators and mimetics thereof.

Pharmaceutical Compositions

In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for 5 oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various 10 buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of 15 polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's 20 Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference in their entirety. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

25 Oral dosage forms. Contemplated for use herein are oral solid dosage forms, which are described generally in Chapter 89 of Remington's Pharmaceutical Sciences (1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein incorporated by reference in its entirety. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets

or pellets. Also, liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with 5 various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Bunker and C. T. Rhodes, herein incorporated by reference in its entirety. In general, the formulation will include the inventive compound, and inert ingredients 10 which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

Also specifically contemplated are oral dosage forms of the above inventive compounds. If necessary, the compounds may be chemically modified so that oral delivery is efficacious. Generally, the chemical 15 modification contemplated is the attachment of at least one moiety to the compound molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently 20 attached vehicles in this invention may also be used for this purpose.

Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981), 25 Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY, , pp. 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin 5 formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

The compounds of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of 10 particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the protein (or derivative) may be formulated (such as by liposome or 15 microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the compound of the invention with an inert material. These diluents could include 20 carbohydrates, especially mannitol, α -lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

25 Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange

peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or 5 tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl 10 cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants 15 may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of 20 various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

25 To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms; e.g., gums. Slowly degenerating matrices may also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compounds of this invention is by a method based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

Other coatings may be used for the formulation. These include a variety of sugars which could be applied in a coating pan. The therapeutic agent could also be given in a film coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan coater or in a fluidized bed or by compression coating.

Pulmonary delivery forms. Also contemplated herein is pulmonary delivery of the present protein (or derivatives thereof). The protein (or derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. (Other reports of this include Adjei *et al.*, Pharma. Res. (1990) 7: 565-9; Adjei *et al.* (1990), Internat. J. Pharmaceutics 63: 135-44 (leuprolide acetate); Braquet *et al.* (1989), J. Cardiovasc. Pharmacol. 13 (suppl.5): s.143-146 (endothelin-1); Hubbard *et al.* (1989), Annals Int. Med. 3: 206-12 (α 1-antitrypsin); Smith *et al.* (1989), J. Clin. Invest. 84: 1145-6 (α 1-proteinase); Oswein *et al.* (March 1990), "Aerosolization of Proteins", Proc. Symp. Resp. Drug Delivery II, Keystone, Colorado (recombinant human growth hormone); Debs *et al.* (1988), J. Immunol. 140: 3482-8 (interferon- γ and tumor necrosis factor α) and Platz *et al.*, U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor).

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to diluents, adjuvants and/or carriers useful in therapy.

5 The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10 μm (or microns), most preferably 0.5 to 5 μm , for most effective delivery to the distal lung.

10 Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog).

15 Dextrans, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

20 Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

25 Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive

compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, 5 dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will 10 comprise a finely divided dry powder containing the inventive compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. Nasal delivery of the inventive compound is 15 also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung.

Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is 20 also contemplated.

Dosages. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, 25 time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.

Specific preferred embodiments

The inventors have determined preferred structures for the preferred peptides listed in Table 4 below. The symbol “ Λ ” may be any of the linkers described herein or may simply represent a normal peptide bond (i.e., so that no linker is present). Tandem repeats and linkers are shown separated by dashes for clarity.

Table 4—Preferred embodiments

| Sequence/structure | SEQ ID NO: |
|--|------------|
| LPGCKWDLLIKQWVCDPL- Λ -V ¹ | 44 |
| V ¹ - Λ - LPGCKWDLLIKQWVCDPL | 45 |
| LPGCKWDLLIKQWVCDPL- Λ - | 46 |
| LPGCKWDLLIKQWVCDPL- Λ -V ¹ | |
| V ¹ - Λ - LPGCKWDLLIKQWVCDPL- Λ - | 47 |
| LPGCKWDLLIKQWVCDPL | |
| SADCYFDILTKSDVCTSS- Λ -V ¹ | 48 |
| V ¹ - Λ - SADCYFDILTKSDVCTSS | 49 |
| SADCYFDILTKSDVTSS- Λ - SADCYFDILTKSDVTSS | 50 |
| - Λ -V ¹ | |
| V ¹ - Λ - SADCYFDILTKSDVTSS - Λ - | 51 |
| SADCYFDILTKSDVTSS | |
| FHDCKWDLLTQWVCHGL- Λ -V ¹ | 52 |
| V ¹ - Λ - FHDCKWDLLTQWVCHGL | 53 |
| FHDCKWDLLTQWVCHGL - Λ - | 54 |
| FHDCKWDLLTQWVCHGL - Λ -V ¹ | |
| V ¹ - Λ - FHDCKWDLLTQWVCHGL - Λ - | 55 |
| FHDCKWDLLTQWVCHGL | |

“V¹” is an Fc domain as defined previously herein. In addition to those listed in Table 4, the inventors further contemplate heterodimers in which each strand of an Fc dimer is linked to a different peptide sequence; for example, wherein each Fc is linked to a different sequence selected from Table 2.

All of the compounds of this invention can be prepared by methods described in PCT appl. no. WO 99/25044.

The invention will now be further described by the following working examples, which are illustrative rather than limiting.

EXAMPLE 1**Peptides****5 Peptide Phage Display****1. Magnetic bead preparation****A. Fc-TALL-1 immobilization on magnetic beads**

The recombinant Fc-TALL-1 protein was immobilized on the Protein A Dynabeads (Dynal) at a concentration of 8 µg of Fc-TALL-1 per 100 µl of the 10 bead stock from the manufacturer. By drawing the beads to one side of a tube using a magnet and pipetting away the liquid, the beads were washed twice with the phosphate buffer saline (PBS) and resuspended in PBS. The Fc-TALL-1 protein was added to the washed beads at the above concentration and incubated with rotation for 1 hour at room temperature. The Fc-TALL-1 coated beads were 15 then blocked by adding bovine serum albumin (BSA) to 1% final concentration and incubating overnight at 4 °C with rotation. The resulting Fc-TALL-1 coated beads were then washed twice with PBST (PBS with 0.05% Tween-20) before being subjected to the selection procedures.

B. Negative selection bead preparation

20 Additional beads were also prepared for negative selections. For each panning condition, 250 µl of the bead stock from the manufacturer was subjected to the above procedure (section 1A) except that the incubation step with Fc-TALL-1 was omitted. In the last washing step, the beads were divided into five 50 µl aliquots.

25 2. Selection of TALL-1 binding phage**A. Overall strategy**

Two filamentous phage libraries, TN8-IX (5×10^9 independent 30 transformants) and TN12-I (1.4×10^9 independent transformants) (Dyax Corp.), were used to select for TALL-1 binding phage. Each library was subjected to either pH 2 elution or 'bead elution' (section 2E). Therefore, four different panning conditions were carried out for the TALL-1 project (TN8-IX using the

pH2 elution method, TN8-IX using the bead elution method, TN12-I the using pH2 elution method, and TN12-I using the bead elution method). Three rounds of selection were performed for each condition.

B. Negative selection

5 For each panning condition, about 100 random library equivalent (5×10^{11} pfu for TN8-IX and 1.4×10^{11} pfu for TN12-I) was aliquoted from the library stock and diluted to 300 μ l with PBST. After the last washing liquid was drawn out from the first 50 μ l aliquot of the beads prepared for negative selections (section 1B), the 300 μ l diluted library stock was added to the beads. The resulting 10 mixture was incubated for 10 minutes at room temperature with rotation. The phage supernatant was drawn out using the magnet and added to the second 50 μ l aliquot for another negative selection step. In this way, five negative selection steps were performed.

C. Selection using the Fc-TALL-1 protein coated beads

15 The phage supernatant after the last negative selection step (section 1B) was added to the Fc-TALL-1 coated beads after the last washing step (section 1A). This mixture was incubated with rotation for two hours at room temperature, allowing specific phage to bind to the target protein. After the supernatant is discarded, the beads were washed seven times with PBST.

D. pH2 elution of bound phage

20 After the last washing step (section 2C), the bound phages were eluted from the magnetic beads by adding 200 μ l of CBST (50 mM sodium citrate, 150 mM sodium chloride, 0.05% Tween-20, pH2). After 5 minute incubation at room temperature, the liquid containing the eluted phage were drawn out and transferred 25 to another tube. The elution step was repeated again by adding 200 μ l of CBST and incubating for 5 minutes. The liquids from two elution steps were added together, and 100 μ l of 2 M Tris solution (pH 8) was added to neutralize the pH. 30 500 μ l of Min A Salts solution (60 mM K_2HPO_4 , 33 mM KH_2PO_4 , 7.6 mM $(NH_4)SO_4$, and 1.7 mM sodium citrate) was added to make the final volume to 1 ml.

E. 'bead elution'

After the final washing liquid was drawn out (section 2C), 1 ml of Min A salts solution was added to the beads. This bead mixture was added directly to a concentrated bacteria sample for infection (section 3A and 3B).

5 3. Amplification

A. Preparation of plating cells

Fresh *E. Coli* (XL-1 Blue MRF') culture was grown to $OD_{600} = 0.5$ in LB media containing 12.5 $\mu g/ml$ tetracycline. For each panning condition, 20 ml of this culture was chilled on ice and centrifuged. The bacteria pellet was 10 resuspended in 1 ml of the Min A Salts solution.

B. Transduction

Each mixture from different elution methods (section 2D and 2E) was added to a concentrated bacteria sample (section 3A) and incubated at 37 °C for 15 minutes. 2 ml of NZCYM media (2XNZCYM, 50 $\mu g/ml$ ampicillin) was 15 added to each mixture and incubated at room temperature for 15 minutes. The resulting 4 ml solution was plated on a large NZCYM agar plate containing 50 $\mu g/ml$ ampicillin and incubated overnight at 37 °C.

C. Phage Harvesting

Each of the bacteria/phage mixture that was grown overnight on a large 20 NZCYM agar plate (section 3B) was scraped off in 35 ml of LB media, and the agar plate was further rinsed with additional 35 ml of LB media. The resulting bacteria/phage mixture in LB media was centrifuged to pellet the bacteria away. 50 ml the of the phage supernatant was transferred to a fresh tube, and 12.5 ml of PEG solution (20% PEG8000, 3.5M ammonium acetate) was added and incubated 25 on ice for 2 hours to precipitate phages. Precipitated phages were centrifuged down and resuspended in 6 ml of the phage resuspension buffer (250 mM NaCl, 100 mM Tris pH8, 1 mM EDTA). This phage solution was further purified by centrifuging away the remaining bacteria and precipitating the phage for the second time by adding 1.5 ml of the PEG solution. After a centrifugation step, the 30 phage pellet was resuspended in 400 μl of PBS. This solution was subjected to a final centrifugation to rid of remaining bacteria debris. The resulting phage

preparation was titered by a standard plaque formation assay (Molecular Cloning, Maniatis et al 3rd Edition).

4. Two more rounds of selection and amplification.

In the second round, the amplified phage (10^{10} pfu) from the first round (section 3C) was used as the input phage to perform the selection and amplification steps (sections 2 and 3). The amplified phage (10^{10} pfu) from the 2nd round in turn was used as the input phage to perform 3rd round of selection and amplification (sections 2 and 3). After the elution steps (sections 2D and 2E) of the 3rd round, a small fraction of the eluted phage was plated out as in the plaque formation assay (section 3C). Individual plaques were picked and placed into 96 well microtiter plates containing 100 μ l of TE buffer in each well. These master plates were incubated in a 37 °C incubator for 1 hour to allow phages to elute into the TE buffer.

5. Clonal analysis (Phage ELISA and sequencing)

The phage clones were analyzed by phage ELISA and sequencing methods. The sequences were ranked based on the combined results from these two assays.

A. Phage ELISA

An XL-1 Blue MRF' culture was grown until OD₆₀₀ reaches 0.5. 30 μ l of this culture was aliquoted into each well of a 96 well microtiter plate. 10 μ l of eluted phage (section 4) was added to each well and allowed to infect bacteria for 15 min at room temperature. 130 μ l of LB media containing 12.5 μ g/ml of tetracycline and 50 μ g/ml of ampicillin was added to each well. The microtiter plate was then incubated overnight at 37 °C. The recombinant TALL-1 protein (1 μ g/ml in PBS) was allowed to coat onto the 96-well Maxisorp plates (NUNC) overnight and 4°C. As a control, the recombinant Fc-Trail protein was coated onto a separate Maxisorp plate at the same molar concentration as the TALL-1 protein.

On the following day, liquids in the protein coated Maxisorp plates were discarded, and each well was blocked with 300 μ l of 2% BSA solution at 37 °C

for one hour. The BSA solution was discarded, and the wells were washed three times with the PBST solution. After the last washing step, 50 μ l of PBST was added to each well of the protein coated Maxisorp plates. Each of the 50 μ l overnight cultures in the 96 well microtiter plate was transferred to the

5 corresponding wells of the TALL-1 coated plates as well as the control Fc-Trail coated plates. The 100 μ l mixtures in the two kinds of plates were incubated for 1 hour at room temperature. The liquid was discarded from the Maxisorp plates, and the wells were washed five times with PBST. The HRP-conjugated anti-M13 antibody (Pharmacia) was diluted to 1:7,500, and 100 μ l of the diluted solution

10 was added to each well of the Maxisorp plates for 1 hour incubation at room temperature. The liquid was again discarded and the wells were washed seven times with PBST. 100 μ l of tetramethylbenzidine (TMB) substrate (Sigma) was added to each well for the color reaction to develop, and the reaction was stopped with 50 μ l of the 5 N H₂SO₄ solution. The OD₄₅₀ was read on a plate

15 reader (Molecular Devices).

B. Sequencing of the phage clones.

For each phage clone, the sequencing template was prepared by a PCR method. The following oligonucleotide pair was used to amplify about 500 nucleotide fragment:

20 primer #1 (5'-CGCGCGCAACTATCGGTATCAAGCTG-3') (SEQ ID NO: 56) and primer #2 (5'-CATGTACCGTAACACTGAGTTTCGTC-3'). (SEQ ID NO: 57) The following mixture was prepared for each clone.

| Reagents | volume (μ L) / tube |
|---|--------------------------|
| dH ₂ O | 26.25 |
| 50% glycerol | 10 |
| 10B PCR Buffer (w/o MgCl ₂) | 5 |
| 25 mM MgCl ₂ | 4 |
| 10 mM dNTP mix | 1 |
| 100 μ M primer 1 | 0.25 |
| 100 μ M primer 2 | 0.25 |
| Taq polymerase | 0.25 |
| Phage in TE (section 4) | 3 |
| Final reaction volume | 50 |

The thermocycler (GeneAmp PCR System 9700, Applied Biosystems) was used to run the following program: 94°C for 5 min; [94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec.]x30 cycles; 72°C for 7 min; cool to 4°C. The PCR product was checked by running 5 µl of each PCR reaction on a 1% agarose gel. The PCR product in the remaining 45 µl from each reaction was cleaned up using the 5 QIAquick Multiwell PCR Purification kit (Qiagen), following the manufacturer's protocol. The resulting product was then sequenced using the ABI 377 Sequencer (Perkin-Elmer) following the manufacturer recommended protocol.

10 6. Sequence ranking and consensus sequence determination

A. Sequence ranking

The peptide sequences that were translated from variable nucleotide sequences (section 5B) were correlated to ELISA data. The clones that showed high OD₄₅₀ in the TALL-1 coated wells and low OD₄₅₀ in the Fc-Trail coated wells were considered more important. The sequences that occur multiple times 15 were also considered important. Candidate sequences were chosen based on these criteria for further analysis as peptides or peptibodies. Five and nine candidate peptide sequences were selected from the TN8-IX and TN12-I libraries, respectively.

20 B. Consensus sequence determination

The majority of sequences selected from the TN12-I library contained a very conserved DBL motif. This motif was also observed in sequences selected from the TN8-IB library as well. Another motif, PFPWE (SEQ ID NO: 110) was also observed in sequences obtained from the TN8-IB library.

25 A consensus peptide, FHDCKWDILLTKQWVCHGL (SEQ ID NO: 58), was designed based on the DBL motif. Since peptides derived from the TN12-I library were the most active ones, the top 26 peptide sequences based on the above ranking criteria (section 5A) were aligned by the DBL motif. The underlined "core amino acid sequence" was obtained by determining the amino 30 acid that occur the most in each position. The two cysteines adjacent to the core

sequences were fixed amino acids in the TN12-I library. The rest of the amino acid sequence in the consensus peptide is taken from one of the candidate peptides, TALL-1-12-10 (Table 2, SEQ ID NO: 37). The peptide and peptibody that was derived from this consensus sequence were most active in the B cell proliferation assay.

EXAMPLE 2

Peptibodies

A set of 12 TALL-1 inhibitory peptibodies (Table 5) was constructed in which a monomer of each peptide was fused in-frame to the Fc region of human IgG1. Each TALL-1 inhibitory peptibody was constructed by annealing the pairs of oligonucleotides shown in Table 6 to generate a duplex encoding the peptide and a linker comprised of 5 glycine residues and one valine residue as an NdeI to SallI fragment. These duplex molecules were ligated into a vector (pAMG21-RANK-Fc, described herein) containing the human Fc gene, also digested with NdeI and SallI. The resulting ligation mixtures were transformed by electroporation into E. coli strain 2596 cells (GM221, described herein). Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected for each of the peptibodies. The nucleotide and amino acid sequences of the fusion proteins are shown in Figure 4A through 4F.

Table 5. Peptide sequences and oligonucleotides used to generate TALL-1 inhibitory peptibodies.

| Peptibody | Peptibody SEQ ID NO | Peptide Sequence | Sense oligo-nucleotide | Antisense oligo-nucleotide |
|---------------|---------------------|---------------------|------------------------|----------------------------|
| TALL-1-8-1-a | 29 | PGTCFPFPWECTHA | 2517-24 | 2517-25 |
| TALL-1-8-2-a | 30 | WGACWPFPWECFKE | 2517-26 | 2517-27 |
| TALL-1-8-4-a | 31 | VPFC DLLTKHCFEA | 2517-28 | 2517-29 |
| TALL-1-12-4-a | 32 | GSRCKYKWDVLTQCFHH | 2517-30 | 2517-31 |
| TALL-1-12-3-a | 33 | LPGCKW DLLIKQWVCDPL | 2517-32 | 2517-33 |
| TALL-1-12-5-a | 34 | SADCYFDILTKSDVCTSS | 2517-34 | 2517-35 |
| TALL-1-12-8-a | 35 | SDDCMYDQLTRMFICSNL | 2517-36 | 2517-37 |
| TALL-1-12-9-a | 36 | DLNCKYDELTYKEWCQFN | 2521-92 | 2521-93 |

| | | | | |
|------------------|----|---------------------|---------|---------|
| TALL-1-12-10-a | 37 | FHDCKYDLLTRQMVCVHGL | 2521-94 | 2521-95 |
| TALL-1-12-11-a | 38 | RNHCFWDHLLKQDICPSP | 2521-96 | 2521-97 |
| TALL-1-12-14-a | 39 | ANQCWWDSLTKKNVCEFF | 2521-98 | 2521-99 |
| TALL-1-consensus | 58 | FHDCKWDLTQWVCHGL | 2551-48 | 2551-49 |

Table 5B TALL-1 inhibitory peptibodies.

| Peptibody | Peptibody SEQ ID NO | Peptide Sequence |
|---------------|---------------------|--|
| TALL-1-8-1-a | 111 | MPGTCPFPW ECTHAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPFPKPD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQOPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK |
| TALL-1-8-2-a | 112 | MWGACWPFPW ECFKEGGGGG VDKTHTCPPC PAPELLGGPS VFLFPFPKPD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQOPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK |
| TALL-1-8-4-a | 113 | MVPFCDLLTK HCFEAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPFPKPD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQOPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK |
| TALL-1-12-4-a | 114 | MGSRCKYKWD VLTKQCFHHG GGGGVDKTHT CPPCPAPELL GGPSVFLFP KPKDTLMISR TPEVTCVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTOKSLSLSP GK |
| TALL-1-12-3-a | 115 | MLPGCKWDLL IKQWVCDPLG GGGGVDKTHT CPPCPAPELL GGPSVFLFP KPKDTLMISR TPEVTCVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTOKSLSLSP GK |
| TALL-1-12-5-a | 116 | MSADCYFDIL TKSDVCTSSG GGGG VDKTHT CPPCPAPELL GGPSVFLFP KPKDTLMISR TPEVTCVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTOKSLSLSP GK |
| TALL-1-12-8-a | 117 | MSDDCMYDQL TRMFICSNLG GGGGVDKTHT CPPCPAPELL GGPSVFLFP KPKDTLMISR TPEVTCVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP |

| | | |
|-------------------------------|-----|--|
| | | PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1-12-9-a | 118 | MDLNCKYDEL TYKEWCQFNG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1-12-10-a | 119 | MFHDCKYDLL TRQMVCVHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1-12-11-a | 120 | MRNHCFWDHL LKQDICPSPG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1-12-14-a | 121 | MANQCWDSDL TKKNVCEFFG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1-consensus | 122 | MFHDCKWDLL TKQWVCHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK |
| TALL-1 12-3 tandem dimer | 123 | MLPGCKWDLL IKQWVCDPLG SGSATGGSGS TASSGSGSAT HMLPGCKWDL LIKQWVCDPL GGGGVDKTH TCPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWLN NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFP SDIAVEWESN QPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMEALHN HYTQKSLSLSP PGK |
| TALL-1 consensus tandem dimer | 124 | MFHDCKWDLL TKQWVCHGLG SGSATGGSGS TASSGSGSAT HMFHDCKWDL LTKQWVCHGL GGGGVDKTH TCPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWLN NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFP SDIAVEWESN QPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMEALHN HYTQKSLSLSP PGK |

Table 6. Sequences of oligonucleotides used in peptibody construction.

| Oligo-nucleotide ID number | SEQ ID NO | Sequence |
|----------------------------|-----------|--|
| 2517-24 | 71 | TAT GCC GGG TAC TTG TTT CCC GTT CCC GTG GGA ATG CAC TCA CGC TGG TGG AGG CGG TGG GG |
| 2517-25 | 72 | TCG ACC CCA CCG CCT CCT GGA GCG TGA GTG CAT TCC CAC GGG AAG CCG AAA CAA GTA CCC GGC A |
| 2517-26 | 73 | TAT GTG GGG TGC TTG TTG GCC GTT CCC GTG GGA ATG TTT CAA AGA AGG TGG AGG CGG TGG GG |
| 2517-27 | 74 | TCG ACC CCA CCG CCT CCA CCT TCT TTG AAA CAT TCC CACGGG AAC GGC CAA CAAGCA CCC CAC A |
| 2517-28 | 75 | TAT GGT TCC GTT CTG TGA CCT GCT GAC TAA ACA CTG TTT CGA AGC TGG TGG AGG CGG TGG GG |
| 2517-29 | 76 | TCG ACC CCA CCG CCT CCA CCA GCT TCG AAA CAG TGT TTA GTC AGC AGG TCA CAGAAC GGA ACC A |
| 2517-30 | 77 | TAT GGG TTC TCG TTG TAA ATA CAA ATG GGA CGT TCT GAC TAA ACA GTG TTT CCA CCA CGG TGG AGG CGG TGG GG |
| 2517-31 | 78 | TCG ACC CCA CCG CCT CCA CCG TGG TGG AAA CAC TGT TTA GTC AGA ACG TCC CAT TTG TAT TTA CAA CGA GAA CCC A |
| 2517-32 | 79 | TAT GCT GCC GGG TTG TAA ATG GGA CCT GCT GAT CAA ACA GTG GGT TTG TGA CCC GCT GGG TGG AGG CGG TGG GG |
| 2517-33 | 80 | TCG ACC CCA CCG CCT CCA CCC AGC GGG TCA CAA ACC CAC TGT TTG ATC AGC AGG TCC CAT TTA CAA CCC GGC AGC A |
| 2517-34 | 81 | TAT GTC TGC TGA CTG TTA CTT CGA CAT CCT GAC TAA ATC TGA CGT TTG TAC TTC TTC TGG TGG AGG CGG TGG GG |
| 2517-35 | 82 | TCG ACC CCA CCG CCT CCA CCA GAA GAA GTA CAA ACG TCA GAT TTA GTC AGG ATG TCG AAG TAA CAG TCA GCA GAC A |
| 2517-36 | 83 | TAT GTC TGA CGA CTG TAT GTA CGA CCA GCT GAC TCG TAT GTT CAT CTG TTC TAA CCT GGG TGG AGG CGG TGG GG |
| 2517-37 | 84 | TCG ACC CCA CCG CCT CCA CCC AGG TTA GAA CAG ATG AAC ATA CGA GTC AGC TGG TCG TAC ATA CAG TCG TCA GAC A |
| 2521-92 | 85 | TAT GGA CCT GAA CTG TAA ATA CGA CGA ACT GAC TTA CAA AGA ATG GTG TCA GTT CAA CGG TGG AGG CGG TGG GG |
| 25221-93 | 86 | TCG ACC CCA CCG CCT CCA CCG TTG AAC TGA CAC CAT TCT TTG TAA GTC AGTCG TCG TAT TTA CAG TTC AGG TCC A |
| 2521-94 | 87 | TAT GTT CCA CGA CTG TAA ATA CGA CCT GCT GAC TCG TCA GAT GGT TTG TCA CGG TCT GGG TGG AGG CGG TGG GG |
| 2521-95 | 88 | TCG ACC CCA CCG CCT CCA CCC AGA CGG TGA CAA ACC ATC TGA CGA GTC AGC AGG TCG TAT TTA CAG TCG TGG AAC A |
| 2521-96 | 89 | TAT GCG TAA CCA CTG TTT CTG GGA CCA CCT GCT GAA ACA |

| | | |
|---------|----|--|
| | | GGA CAT CTG TCC GTC TCC GGG TGG AGG CGG TGG GG |
| 2521-97 | 90 | TCG ACC CCA CCG CCT CCA CCC GGA GAC GGA CAG ATG TCC TGT TTC AGC AGG TGG TCC CAG AAA CAG TGG TTA CGC A |
| 2521-98 | 91 | TAT GGC TAA CCA GTG TTG GTG GGA CTC TCT GCT GAA AAA AAA CGT TTG TGA ATT CTT CGG TGG AGG CGG TGG GG |
| 2521-99 | 92 | TCG ACC CCA CCG CCT CCA CGG AAG AAT TCA CAA ACG TTT TTT TTC AGC AGA GAG TCC CAC CAA CAC TGG TTA GCC A |
| 2551-48 | 93 | TAT GTT CCA CGA CTG CAA ATG GGA CCT GCT GAC CAA ACA GTG GGT TTG CCA CGG TCT GGG TGG AGG CGG TGG GG |
| 2551-49 | 94 | TCG ACC CCA CCG CCT CCA CCC AGA CGG TGG CAA ACC CAC TGT TTG GTC AGC AGG TCC CAT TTG CAG TCG TGG AAC A |

pAMG21-RANK-Fc vector

pAMG21. The expression plasmid pAMG21 (ATCC accession no. 98113) can be derived from the Amgen expression vector pCFM1656 (ATCC #69576) which in turn be derived from the Amgen expression vector system described in US Patent No. 4,710,473. The pCFM1656 plasmid can be derived from the described pCFM836 plasmid (U.S. Patent No. 4,710,473) by:

10 • destroying the two endogenous NdeI restriction sites by end filling with T4 polymerase enzyme followed by blunt end ligation;

 • replacing the DNA sequence between the unique AatII and ClaI restriction sites containing the synthetic P_L promoter with a similar fragment obtained from pCFM636 (patent No. 4,710,473) containing the P_L promoter (see SEQ ID NO: 95 below); and

15 • substituting the small DNA sequence between the unique ClaI and KpnI restriction sites with the oligonucleotide having the sequence of SEQ ID NO: 96.

SEQ ID NO: 95:

AatII
 5' CTAATTCCGCTCTCACCTACCAAACAATGCCCTGCAAAAAATAATTAT-
 20 3' TGCAGATTAAGGCGAGAGTGGATGGTTACGGGGGACGTTTATTTAAGTATA-
 -AAAAAACATACAGATAACCATCTGCGGTGATAAAATTATCTGGCGGTGTTGACATAAA-
 -TTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACGCCACAACGTATTT-
 25 -TACCACTGGCGGTGATACTGAGCACAT 3'
 -ATGGTGACCGCCACTATGACTCGTGTAGC 5'
 ClaI

SEQ ID NO: 96:

5' CGATTGATTCTAGAAGGAGGAATAACATATGGTTAACCGCGTTGGAATTCGGTAC
 3'
 3' TAAACTAAGATCTTCCTCCTATTGTATACCAATTGCGAACCTTAAGC 5'
Clal KpnI

5

The expression plasmid pAMG21 can then be derived from pCFM1656 by making a series of site-directed base changes by PCR overlapping oligonucleotide mutagenesis and DNA sequence substitutions. Starting with the BglII site (plasmid bp # 180) immediately 5' to the plasmid replication promoter P_{copB} and proceeding toward the plasmid replication genes, the base pair changes are as shown in Table 7 below.

10

Table 7—Base pair changes resulting in pAMG21

| | <u>pAMG21 bp #</u> | <u>bp in pCFM1656</u> | <u>bp changed to in pAMG21</u> |
|----|--------------------|---------------------------|--------------------------------|
| 15 | # 204 | T/A | C/G |
| | # 428 | A/T | G/C |
| | # 509 | G/C | A/T |
| | # 617 | -- | insert two G/C bp |
| 20 | # 679 | G/C | T/A |
| | # 980 | T/A | C/G |
| | # 994 | G/C | A/T |
| | # 1004 | A/T | C/G |
| | # 1007 | C/G | T/A |
| 25 | # 1028 | A/T | T/A |
| | # 1047 | C/G | T/A |
| | # 1178 | G/C | T/A |
| | # 1466 | G/C | T/A |
| | # 2028 | G/C | bp deletion |
| 30 | # 2187 | C/G | T/A |
| | # 2480 | A/T | T/A |
| | # 2499-2502 | <u>AGTG</u> TCAC | <u>GTCA</u> CAGT |
| 35 | # 2642 | <u>TCCGAGC</u> AGGCTCG | 7 bp deletion |
| | # 3435 | G/C | A/T |
| 40 | # 3446 | G/C | A/T |
| | # 3643 | A/T | T/A |

The DNA sequence between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites is substituted with the DNA sequence below (SEQ ID NO: 97):

[AatII sticky end] 5' GCGTAACGTATGCATGGCTCC-
 (position #4358 in pAMG21) 3' TGCACGCATTGCATACGTACCAAGAGG-

5 -CCATGCGAGAGTAGGGAACGTGCCAGGCATCAAATAAAACGAAAGGCTAGTCGAAAGACT-
 -GGTACGCTCTCATCCCTGACGGTCCGTAGTTATTTGCTTCCGAGTCAGCTTCTGA-

10 -GGGCCTTCGTTTATCTGTTGTTGCGTGAACGCTCCCTGAGTAGGACAAATCCGC-
 -CCCGAAAGCAAATAGACAACAAACAGCCACTGCGAGAGGACTCATCCTGTTAGGCG-

15 -CGGGAGCGGATTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCGC-
 -GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGCCTCCCACCGCCCTGCGGGCG-

20 -CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTGCCT-
 -GTATTTGACGGTCCGTAGTTAATTGCTTCCGGTAGGACTGCCTACCGAAAAACGCA-

25 AatII
 -TTCTACAAACTCTTTGTTTATTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-
 -AAGATGTTGAGAAAACAAATAAAAGATTATGTAAGTTATACCTGCAGCATGAATTG-

30 -TTTAAAGTATGGCAATCAATTGCTCTGTTAAAATTGCTTAGAAATACTTGGCAGC-
 -AAAATTCTACCCGTTAGTTAACGAGGACAATTAAACGAAATCTTATGAAACCGTCG-

35 -GGTTGTTGATTGAGTTCATTTGCGCATTGGTAAATGAAAGTGACCGTGCCTTAC-
 -CCAAACAAACATAACTCAAAGTAAACCGTAACCAATTACCTTCACTGGCACGCGAATG-

40 -TACAGCCTAATATTTGAAATATCCAAGAGCTTTCCCTCGCATGCCACGCTAAAC-
 -ATGTCGGATTATAAAACTTATAGGGTTCTCGAAAAGGAAGCGTACGGTGCATTG-

45 -ATTCTTTCTCTTTGGTTAAATCGTTGTTGATTTATTATTTGCTATATTATTTTC-
 -TAAGAAAAGAGAAAACCAATTAGCAACAAACTAAATAAAACGATATAAAATAAAAG-

50 -GATAATTATCAACTAGAGAAGGAACAATTAAATGGTATGTTCATACACGCATGAAAAATA-
 -CTATTAATAGTTGATCTCTCCTGTTAATTACCATACAAGTATGTCGTACATTTTTAT-

55 -AACTATCTATATAGTTGCTTCTGAAATGTGCAAAACTAACGATTCCGAAGCCATTAT-
 -TTGATAGATATCAACAGAAAGAGACTTACACGTTTGATTGTAAGGCTTCGGTAATA-

60 -TAGCAGTATGAATAGGAAACTAAACCCAGTGATAAGACCTGATGATTGCTTCTTTAA-
 -ATCGTCATACTTATCCCTTGATTGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-

65 -TTACATTGGAGATTTTTATTTACAGCATTGTTCAAATATATTCCAATTAAATCGGTG-
 -AATGAAACCTCTAAAAATAATGTCGTAACAAAGTTATATAAGGTTAATTAGCCAC-

70 -AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTAAATTAGCGTCATCAT-
 -TTACTAACCTCAATCTATTAGATGATCCTAGTATAAAATAATTAAATCGCAGTAGTA-

75 -AATATTGCGCTCCATTAGGGTAATTATCCAGAATTGAAATATCAGATTAAACCATAG-
 -TTATAACGGAGGTAAAAACCCATTAAATAGGTCTTAACCTTATAGCTAAATTGGTATC-

80 -AATGAGGATAAAATGATCGCGAGTAAATAATATTCAACATGTACCATTTAGTCATATCAG-
 -TTACTCCTATTACTAGCGCTCATTTATTAAAGTGTACATGGTAAATCAGTATAGTC-

85 -ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTAAATTATTCTGT-
 -TATTGCTAACTAATTATAGTAATAACGAAGATGTCGAAATTAAATAATTAAAGACA-

90 -AAGTGTGCGCGATTATGCTTCTACCCATCTCTTTATCCTTACCTATTGTTGTC-
 -TTCACAGCAGCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-

95 -GCAAGTTTGCCTGTTATATATCATTAAAACGGAATAGATTGACATTGATTCTAATAA-
 -CGTTCAAAACGCACAATATAGTAATTGCTTACCTAATGTAACCTGAAACTAAGATTAT-

100 -ATTGGATTGGTCACACTATTATCGCTTGAACATAACATTGTTAACATAAGTACCTG-
 -TAACCTAAAACAGTGTGATAATAGCGAACTTATGTTAACAAATTGTATTGAC-

-TAGGATCGTACAGGTTACGCAAGAAAATGGTTGTTAGTCGATTAATCGATTGATT-
 -ATCCTAGCATGTCATGCGTTCTTACCAACAATATCAGCTAATTAGCTAACTAA-
 -CTAGATTGTTAACTAATTAAAGGAGGAATAACATATGGTTAACCGGTTGGAATTGCA-
 5 -GATCTAAACAAAATTGATTAATTCCCTTATTGTATACCAATTGCGAACCTTAAGCT-

 10 **SacII**
 -GCTCACTAGTGTGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGGGAAAGAA-
 -CGAGTGATCACAGCTGGACGTCCCAGGTACCTTCGAATGAGCTCCTAGGCGCTTCTT-
 -GAAGAAGAAGAAGAAAGCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
 -CTTCTTCTTCTTCGGCTTCCTCGACTCAACCGACGACGGTGGCAGCTCGTTAT-
 -ACTAGCATAACCCCTGGGGCCTCTAAACGGGCTTGAGGGGTTTGCTGAAAGGAGG-
 15 -TGATCGTATTGGGAACCCGGAGATTGCCAGAACTCCCCAAAAACGACTTCCTCC-
 -AACCGCTCTTCAGCCTTCACGC 3' **[SacII sticky end]**
 -TTGGCGAGAAGTGCAGAAGTG 5' **(position #5904 in pAMG21)**

20 During the ligation of the sticky ends of this substitution DNA sequence, the outside AatII and SacII sites are destroyed. There are unique AatII and SacII sites in the substituted DNA.

25 A gene encoding human RANK fused to the N-terminus of Fc was ligated into pAMG21 as an NdeI to BamHI fragment to generate Amgen Strain #4125. This construct was modified to insert a valine codon at the junction of RANK and Fc. The adjacent valine and aspartate codons create a unique SalI site. This allows for the fusion of peptides at the N-terminus of Fc3 between the unique NdeI and SalI sites. The RANK sequence is deleted upon insertion of a new NdeI-SalI fragment. The sequence of the vector is given in Figure 5A through 5M.

30 GM221 (Amgen #2596). The Amgen host strain #2596 is an E. coli K-12 strain derived from Amgen strain #393, which is a derivative of E. coli W1485, obtained from the E. coli Genetic Stock Center, Yale University, New Haven, Connecticut (CGSC strain 6159). It has been modified to contain both the temperature sensitive lambda repressor cI857s7 in the early ebg region and the lacI^Q repressor in the late ebg region (68 minutes). The presence of these two repressor genes allows the use of this host with a variety of expression systems, however both of these repressors are irrelevant to the expression from luxP_R. The untransformed host has no antibiotic resistances.

40 The ribosome binding site of the cI857s7 gene has been modified to include an enhanced RBS. It has been inserted into the ebg operon between

nucleotide position 1170 and 1411 as numbered in Genbank accession number M64441Gb_Ba with deletion of the intervening ebg sequence. The sequence of the insert is shown below with lower case letters representing the ebg sequences flanking the insert shown below (SEQ ID NO: 98):

5

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ttttttcggtGCGGCCGCACCATTATCACCGCCAGAGGTAAACTAGTCAACACGCACGGTGTAGATAT
TTATCCCTGCGGTGATAGATTGAGCACATCGATTGATTCTAGAAGGAGGGATAATATATGAG
CACAAAAAAAGAAACCATTAAACACAAGAGCAGCTGAGGACGCACGTCGCCCTAAAGCAATTAA
TGAAAAAAAGAAAAATGAACCTGGCTTATCCCAAGGAATCTGTCGAGACAAGATGGGGATGGG
10  GCAGTCAGGCCTGGTGTCTTATTAATGGCATCAATGCATTAATGCTTATAACGCCGCATTGC
TTACAAAAATTCTCAAAGTTAGCGTTGAAGAAATTAGCCCTCAATGCCAGAGAAATCTACGAG
ATGTATGAAGCGGTTAGTATGCAGCCGTCACTAGAAGTGAAGTATGAGTACCCGTTTTCTCA
TGTCAGGCAGGGATGTTCTCACCTAACGTTAGAACCTTACCAAAGGTGATGCCAGAGAGATGG
15  GTAAGCACAACCAAAAAAGCCAGTGAATTCTGCATTCGGCTTGGTTGAAGGTAAATTCCATGA
CCGCACCAACAGGCTCCAAGCCAAGCTTCGACGGAATGTTAATTCTCGTTGACCCGTGAGCA
GGCTGTTGAGCCAGGTGATTCTGCATAGCCAGACTTGGGGGTGATGAGTTACCTICAAGAAA
CTGATCAGGGATAGCGGTCAAGGTGTTTACAAACCAACTAAACCCACAGTACCCAAATGATCCCAT
GCAATGAGAGTTGTTCCGTTGTGGGGAAAGTTATCGCTAGTCAGTGGCCTGAAGAGAGACGTTGG
20  CTGATAGACTAGTGGATCCACTAGTgttctgccc

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20

The construct was delivered to the chromosome using a recombinant phage called MMebg-cI857s7enhanced RBS #4 into F'tet/393. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM101. F'tet/GM101 was then modified by the delivery of a lacI^Q construct into the ebg operon between nucleotide position 2493 and 2937 as numbered in the Genbank accession number M64441Gb_Ba with the deletion of the intervening ebg sequence. The sequence of the insert is shown below with the lower case letters representing the ebg sequences flanking the insert (SEQ ID NO: 99) shown below:

30

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ggcggaaccGACGTCCATCGAATGGTCAAAACCTTCCGGTATGGCATGATAGCCCGGAAGA
GAGTCATTAGGGTGGTGAATGTAAACCGTAACGTTATACGATGTCGAGAGTATGCCGT
35  GTCTCTTATCAGACCGTTCCCGCGTGGTAACCAGGCCAGCCACGTTCTGCAGAAACGCCGG
AAAAAGTCGAAGCGCGATGGCGAGCTGAATTACATTCCCAACCGCGTGGCACAACAATGG
CGGGCAAAACAGTCGCTCCTGATTGGCGTTGCCACCTCCAGTCTGGCCCTGCACGCCGTGCA
40  AATTCGCGCCGATTAATCTCGCGCGATCAACTGGGTGCCAGCGTGGTGGTGCATGGTA
GAACGAAGCGCGCTCGAACGCTGTAAAGCGCGTGCACAATCTCTCGCGAACCGTCAGTG
GGCTGATCATTAACTATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAAGCTGCCACTAA
TGTTCCGGCGTTATTCGATGTCTGACCAGACACCCATCAACAGTATTATTCCTCCATGA
45  AGACGGTACCGCACTGGCGTGGAGCATCTGGTCGATTGGGTACCCAGCAAATCGCGCTGTTA
GCCGGCCCATTAAGTCTGTCGGCCGCTCGCGTCTGGCTGGCTGGCATAAAATATCTCACTCG
CAATCAAATTAGCCGATAGCGGAACGGGAAGGGCAGTGGAGTGCCATGTCCGTTTCACAA
ACCATGCAAATGCTGAATGAGGGCATGTTCCACTGCGATGCTGGTGCACAGATCAGATGG
CGCTGGCGCAATCGCGCATTACCGAGTCCGGCTGCCGTTGGTGCAGATCTCGGTAGT
GGGATACGACGATACCGAAGACAGCTCATGTTATATCCCGCCGTTAACCAACATCAAACAGGAT
TTCGCCTGCTGGGCAAACCGAGCGTGGACCGCTGCAACTCTCTCAGGGCCAGGCGGTGA

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AGGGCAATCAGCTGTTGCCGTCCTCACTGGTAAAAGAAAAACCACCTGGCGCCAATACGCA
AACCCTCTCCCGCGCGTTGGCGATTCAATTAAATGCAGCTGGCACGACAGGTTCCCGACTGG
AAAGCGGACAGTAAGGTACCATAGGATCCaggcacagga

5 The construct was delivered to the chromosome using a recombinant phage called AGebg-LacIQ#5 into F'tet/GM101. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM221. The F'tet episome was cured from the strain using acridine orange at a concentration of 25 µg/ml in LB. The cured strain was
10 identified as tetracycline sensitive and was stored as GM221.

Expression in *E. coli*. Cultures of each of the pAMG21-Fc-fusion constructs in *E. coli* GM221 were grown at 37 °C in Luria Broth medium. Induction of gene product expression from the luxPR promoter was achieved
15 following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-homoserine lactone to the culture media to a final concentration of 20 ng/ml. Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial cultures were examined by microscopy for the presence of inclusion bodies and were then collected by centrifugation. Refractile inclusion bodies were observed
20 in induced cultures indicating that the Fc-fusions were most likely produced in the insoluble fraction in *E. coli*. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% β-mercaptoethanol and were analyzed by SDS-PAGE. In each case, an intense Coomassie-stained band of the appropriate molecular weight was observed on an SDS-PAGE gel.

25

EXAMPLE 3

TALL-1 peptibody inhibits TALL-1 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).
30 Purified (10^5) B cells were cultured in MEM, 10% heat inactivated FCS, 5×10^{-5} M 2-mercaptoethanol, 100 U/ml penicillin, 100 µg/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml TALL-1 protein and 2 µg/ml of Goat F(ab')₂ anti-mouse IgM (Jackson ImmunoResearch Laboratory,

West Grove, Pennsylvania) with the indicated amount of recombinant TALL-1 peptibody for a period of 4 days at 37 °C, 5%CO₂. Proliferation was measured by the uptake of radioactive ³[H] thymidine after an 18-hour incubation period.

5

EXAMPLE 4

TALL-1 peptibody blocks TALL-1 binding to its receptors

Reacti-Gel 6x (Pierce) were pre-coated with human AGP3 (also known as TALL-1, Khare et al., Proc. Natl. Acad. Sci. 97:3370-3375, 2000) and blocked 10 with BSA. 100 pM and 40 pM of AGP3 peptibody samples were incubated with indicated various concentrations of human AGP3 at room temperature for 8 hours before run through the human AGP3-coated beads. The amount of the bead-bound peptibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody (Jackson Immuno Research). The binding signal is proportional to the 15 concentration of free peptibody at binding equilibrium. Dissociation equilibrium constant (K_D) was obtained from nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody (SEQ ID NO: 123) binding with human AGP3 (Figure 10).

20 To determine if this AGP3 peptibody can neutralize murine AGP3 binding as well as human AGP3, a BIACore neutralizing assay was utilized. All experiments were performed on a BIACore 3000 at room temperature. Human TACI-Fc protein (Xia et al, J. Exp. Med. 192, 137-144, 2000) was immobilized to a B1 chip using 10 mM Acetate pH 4.0 to a level of 2900RU. A blank flow cell 25 was used as a background control. Using a running buffer of PBS (without calcium or magnesium) containing 0.005% P20, 1 nM recombinant human AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with indicated various amount of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed using 8 mM glycine pH 1.5 for 1 minute, 30 25 mM 3-[cyclohexylamino]-1-propanesulfonic acid (CAPS) pH 10.5, 1 M NaCl for 1 minute. For determination of murine AGP3 binding, human his-tagged

TACI was immobilized to 1000 RU in the above buffer. 5 nM recombinant murine AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with the various amounts indicated in Figure 11 of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed with 5 10 mM HCl pH2, twice for 30 seconds. Relative binding of both human and murine AGP3 at presence vs absence of AGP3 peptibody (SEQ ID NO: 123) was measured (y axis). Relative binding response was determined as (RU-RU blank/ RU₀-RU blank). The AGP3 peptibody (SEQ ID NO: 123) inhibited both human and murine AGP3 binding to its receptor TACI (Figures 11A and 11B).

10 To examine if this AGP3 peptibody blocks AGP3 binding to all three receptors (TACI, BCMA and BAFFR), recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. Using 10 mM acetate, pH4, human TACI-Fc was immobilized to 6300 RU, human BCMA-Fc to 5000 RU, and BAFFR-Fc to 6000 RU. 1 nM of recombinant human AGP3 (in 15 running buffer containing 0.1 mg/ml BSA and 0.1 mg/ml Heparin) or 1 nM recombinant APRIL protein (Yu, et al., Nat. Immunol., 1:252-256, 2000) were incubated with indicated amount of AGP3 peptibody before injection over each receptor surface. Regeneration for the AGP3 experiment was done with 8 mM glycine, pH 1.5, for 1 minute, followed by 25 mM CAPS, pH 10.5, 1M NaCl for 1 20 minute. Regeneration for the APRIL experiment was performed with 8 mM glycine, pH 2, for one minute, followed by 25 mM CAPS, pH 10.5, 1 M NaCl for one minute. Relative binding of AGP3 or APRIL was measured. AGP3 peptibody (SEQ ID NO: 123) blocked AGP3 binding to all three receptors (Figure 12A). AGP3 peptibody didn't affect APRIL binding to the receptors (Figure 12B).

25

EXAMPLE 5

AGP3 peptibody blocks AGP3 mediated B cell proliferation

30 Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).

Purified (10^5) B cells were cultured in minimal essential medium (MEM), 10% heat inactivated fetal calf serum (FCS), 5×10^{-5} M 2-mercaptoethanol, 100 U/ml penicillin, 100 μ g/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml AGP3 (TALL-1) protein and 2 μ g/ml of Goat F(ab')₂ 5 anti-mouse IgM (Jackson ImmunoResearch Laboratory, West Grove, Pennsylvania) with the indicated amount of recombinant AGP3 peptibody (SEQ ID NO: 123) for a period of 4 days at 37 °C, 5% CO₂. Proliferation was measured by the uptake of radioactive ³[H] thymidine after an 18-hour incubation period.

10

EXAMPLE 6

AGP3 peptibody on AGP3-stimulated Ig production in mice

Mice (Balb/c females of 9-14 weeks of age and 19-21 g of weight) were purchased from Charles River Laboratories, Wilmington, MA. Mice (n = 10) 15 were treated i.p. with 1 mg/Kg of human AGP3 once a day for five consecutive days followed by 5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or by saline or by 5 mg/Kg of human Fc. Other mice were left untreated. Mice were sacrificed on the sixth day to measure serum IgM and IgA, which were measured by ELISA. Briefly, plates were coated with capture antibodies specific 20 for IgM or IgA (Southern Biotechnology Associates, Birmingham, AL), blocked, and added with dilutions of standard (IgM from Calbiochem, San Diego, CA and IgA from Southern Biotechnology Associates) or test samples. Captured Ig were revealed using biotinylated antibodies specific for IgM or IgA (Southern Biotechnology Associates), neutravidin-conjugated peroxidase (Pierce, Rockford, IL), and tetramethylbenzidine (TMB) microwell peroxidase substrate (KPL, Gaithersburg, MD). Optical densities were quantitated in a Thermomax ELISA reader (Molecular Devices, Menlo Park, CA).

Human AGP3-stimulated increase in serum levels of IgM and IgA was blocked by 5 mg/Kg of the anti-AGP3 peptibody (SEQ ID NO: 123) and not by 30 0.5 mg/Kg (Figures 14A and 14B).

EXAMPLE 7**AGP3 peptibody reduced spleen B cell number in mice**

Mice (as above, n = 7) were treated i.p. for seven consecutive days with 5 mg/Kg or 1.5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or with saline or with 5 mg/Kg of human Fc. Mice were sacrificed on the eighth day to count spleen B cell number. Spleens were collected in saline and gently disrupted by manual homogenization to yield a cell suspension. The total cell number was obtained with a H1E counter (Technicon, Tarrytown, NY). Percentages of B cells were derived by immunofluorescence double staining and flow cytometry using fluorescein isothiocyanate (FITC)-conjugated and phycoerythrin (PE)-conjugated Ab against CD3 and B220, respectively (PharMingen, San Diego, CA) and a FACScan analyser (Becton and Dickinson, Mountain View, CA). B cells were identified for being CD3-B220+. At all doses, the AGP3 peptibody (SEQ ID NO: 123) decreased spleen B cell number in a dose-response fashion (Figure 14) (SEQ ID NO: 123).

EXAMPLE 8**AGP3 peptibody reduced arthritis severity in mouse CIA model**

Eight to 12 week old DBA/1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) were immunized with bovine collagen type II (bCII) (purchased from University of Utah), emulsified in complete Freunds adjuvant (Difco) intradermally at the base of tail. Each injection was 100 μ l containing 100 μ g of bCII. Mice were boosted 3 weeks after the initial immunization with bCII emulsified in incomplete Freunds adjuvant. Treatment was begun from the day of booster immunization for 4 weeks. Mice were examined for the development of arthritis. As described before (Khare et al., *J. Immunol.* 155: 3653-9, 1995), all four paws were individually scored from 0-3. Therefore arthritis severity could vary from 0 to 12 for each animal. AGP3 (SEQ ID NO: 123) peptibody treatment significantly reduced the severity of arthritic scores (Figure 15).

Serum samples were taken one week after final treatment (day 35) for the analysis of anti-collagen antibody level. High binding ELISA plates (Immulon, Nunc) were coated with 50 μ l of 4 μ g/ml solution of bovine CII in carbonate buffer and plated were kept in cold overnight in the refrigerator. Plates were 5 washed three times with cold water. 75 μ l of blocking solution made up of PBS/.05% tween 20/1% BSA was used to block non-specific binding for an hour. Samples were diluted (in blocking buffer) in dilution plates at 1:25, 1:100, 1:400, and 1:1600 and 25 μ l of these samples were added to each well of the ELISA plate for a final dilution of 100, 400, 1600, and 6400 with a final volume of 100 10 μ l/well. After incubation at room temperature for 3 hours, plates were washed three times again. 100 μ l of secondary antibody diluted in blocking buffer (rat anti-mouse IgM, IgG2a, IgG2b, IgG1, IgG3-HRP) was added to each well and plates were incubated for at least 2 hours. Plates were washed four times. 100 μ l 15 of TMB solution (Sigma) was added to each well and the reaction was stopped using 50 μ l of 25% sulfuric acid. Plates were read using an ELISA plate reader at 450 nm. OD was compared with a standard pool representing units/ml. AGP3 peptibody (SEQ ID NO: 123) treatment reduced serum anti-collagen II IgG1, IgG3, IgG2a, and IgG2b levels compared to PBS or Fc control treatment groups (Figure 16).

20

EXAMPLE 9

Treatment of AGP3 peptibody in NZB/NZW lupus mice

Five month old lupus prone NZBx NZBWF1 mice were treated i.p. 25 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody or human Fc proteins. Prior to the treatment, animals were pre-screened for protein in the urine with Albustix reagents strips (Bayer AG). Mice having greater than 100 mg/dl of protein in the urine were not included in the study. Protein in the urine was evaluated monthly throughout the life of the experiment. AGP3 peptibody 30 (SEQ ID NO: 123) treatment led to delay of proteinuria onset and improved survival (Figure 17).

AGP3 peptibody treatment reduced B cell number in mice. Balb/c mice received 7 daily intraperitoneal injections of indicated amount of AGP3 peptibody (SEQ ID NO: 123) or human Fc protein. On day 8, spleens were collected, and subject to FACS analysis for B220+ B cells as set for in Table 8.

5

Table 8
AGP3 Pb Reduces B Cell Number in Normal Mice

| n=7 | dose (1/dayx7) | spleen B cell (1x10 ⁶) | SD | t test |
|-----------|----------------|---------------------------------------|-----|-------------|
| saline | | 51.3 | 9.6 | |
| Fc | 5mg/Kg | 45.5 | 7.1 | |
| Peptibody | 5mg/Kg | 20.1 | 3.8 | 1.37856E-05 |
| | 1.5mg/Kg | 22.6 | 6.9 | 5.10194E-05 |
| | 0.5mg/Kg | 25.8 | 3.6 | 0.000111409 |

10

* * *

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto, without departing from the spirit and scope of the invention as set forth herein.

15

What is claimed is:

1. A TALL-1-binding composition of matter comprising an amino acid sequence Dz²Lz⁴, wherein z² is an amino acid residue and z⁴ is T or I, and wherein the composition of matter does not comprise a fragment of TACI, BCMA, or BAFFR (SEQ ID NOS: 195, 196, and 197).
- 5 2. The composition of matter of Claim 1, wherein z⁴ is T.
3. A TALL-1-binding composition of matter comprising an amino acid sequence Dz²LI, wherein z² is an amino acid residue.
- 10 4. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$$

(SEQ. ID. NO: 100)

wherein:

- 15 a¹, a², a³ are each independently absent or amino acid residues;
- a⁶ is an amino acid residue;
- a⁸ is T or I;
- a⁹ is a basic or hydrophobic residue;
- a¹² is a neutral polar residue; and
- 20 a¹³ and a¹⁴ are each independently absent or amino acid residues.
- 5 5. The composition of matter of Claim 4 wherein a⁸ is T and a⁹ is a basic residue.
6. The composition of matter of Claim 4 wherein a⁹ is K and a¹² is F.
7. The composition of matter of Claim 1 comprising an amino acid
- 25 sequence of the formula

$$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$$

(SEQ. ID. NO: 104)

wherein:

- b¹ and b² are each independently absent or amino acid residues;
- 30 b³ is an acidic or amide residue;

b⁵ is an amino acid residue;

b⁶ is an aromatic residue;

b⁸ is an amino acid residue;

b¹⁰ is T or I;

5 b¹¹ is a basic residue;

b¹² and b¹³ are each independently amino acid residues;

b¹⁴ is a neutral polar residue; and

15 b¹⁶, b¹⁷, and b¹⁸ are each independently absent or amino acid residues.

10 8. The composition of matter of Claim 7 wherein:

b³ is D, Q, or E;

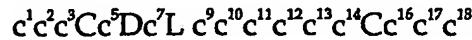
b⁶ is W or Y;

b¹⁰ is T;

b¹¹ is K or R; and

15 b¹⁴ is V or L.

9. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



(SEQ. ID. NO: 105)

20 wherein:

c¹, c², and c³ are each independently absent or amino acid residues;

c⁵ is an amino acid residue;

c⁷ is an amino acid residue;

c⁹ is T or I;

25 c¹⁰ is a basic residue;

c¹¹ and c¹² are each independently amino acid residues;

c¹³ is a neutral polar residue;

c¹⁴ is an amino acid residue;

c¹⁶ is an amino acid residue;

30 c¹⁷ is a neutral polar residue; and

c^{18} is an amino acid residue or is absent.

10. The composition of matter of Claim 9 wherein:

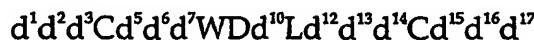
c^9 is T;

c^{10} is K or R;

5 c^{13} is a I, L, or V; and

c^{17} is A or L.

11. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



10 (SEQ. ID. NO: 106)

wherein:

d^1 , d^2 , and d^3 are each independently absent or amino acid residues;

d^5 , d^6 , and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

15 d^{13} is T or I;

d^{14} is an amino acid residue; and

d^{16} , d^{17} , and d^{18} are each independently absent or amino acid residues.

12. The composition of matter of Claim 1 comprising an amino acid sequence of the formula



20 (SEQ. ID. NO: 107)

wherein:

e^1 , e^2 , and e^3 are each independently absent or amino acid residues;

25 e^5 , e^6 , e^7 , e^9 , and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15} , e^{16} , and e^{17} are each independently absent or amino acid residues.

13. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$f^1f^2f^3Kf^4Df^5Lf^6f^{10}Qf^{12}f^{13}f^{14}$

(SEQ ID NO: 109)

5 wherein:

f^1 , f^2 , and f^3 are absent or are amino acid residues;

f^4 is W, Y, or F;

f^5 is an amino acid residue;

f^6 is T or I;

10 f^{10} is K, R, or H;

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent; and

f^{14} is any amino acid residue or is absent;

15 provided that only one of f^1 , f^2 , and f^3 may be C, and only one of f^{12} , f^{13} , and f^{14} may be C.

14. The composition of matter of Claim 13, wherein f^4 is W.

15. The composition of matter of Claim 13, wherein f^5 is L.

16. The composition of matter of Claim 13, wherein f^6 is T.

20 17. The composition of matter of Claim 13, wherein f^{10} is K.

18. The composition of matter of Claim 13, wherein f^{12} is C and one of f^1 , f^2 , and f^3 is C.

19. The composition of matter of Claim 13, wherein f^{13} is V.

20. The composition of matter of Claim 13 comprising an amino acid

25 sequence of the formula

$f^1f^2f^3Kf^4Df^5Lf^6f^{10}Qf^{12}f^{13}f^{14}$

(SEQ ID NO: 125).

21. The composition of matter of Claim 20 comprising an amino acid

sequence selected from the group consisting of SEQ ID NOS: 32, 33, 58,

60, 63, 66, 67, 69, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, and 187.

22. The composition of matter of Claim 20 comprising an amino acid sequence of the formula

LPGCKWDLLIKQWVCDPL (SEQ ID NO: 33).

23. A composition of matter comprising an amino acid sequence of the formula

$g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$

(SEQ. ID. NO: 101)

wherein:

g^1 , g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

15 g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and

g^{14} is absent or is an amino acid residue.

24. The composition of matter of Claim 23 wherein:

g^2 is G;

20 g^5 is W;

g^8 is P;

g^{10} is E; and

g^{13} is a basic residue.

25. A composition of matter comprising an amino acid sequence of the formula

$h^1h^2h^3CWh^6h^7W Gh^{10}Ch^{12}h^{13}h^{14}$

(SEQ. ID. NO: 102)

wherein:

h^1 , h^2 , and h^3 are each independently absent or amino acid residues;

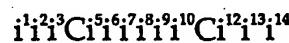
30 h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;
 h^{10} is an acidic or polar hydrophobic residue; and
 h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues.

26. The composition of matter of Claim 25 wherein:

5 h^1 is G;
 h^6 is A;
 h^7 is a neutral polar residue; and
 h^{10} is an acidic residue.

27. A composition of matter comprising an amino acid sequence of the
10 formula



(SEQ. ID. NO: 103)

wherein:

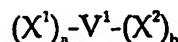
15 i^1 is absent or is an amino acid residue;
 i^2 is a neutral polar residue;
 i^3 is an amino acid residue;
 i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;
 i^9 is an acidic residue;
 i^{10} is an amino acid residue;
20 i^{12} and i^{13} are each independently amino acid residues; and
 i^{14} is a neutral polar residue.

28. The composition of matter of Claim 27 wherein:

i^2 is W; and
 i^{14} is W.

25 29. A TALL-1 binding composition of matter comprising an amino acid sequence
 of the formula PFPWE (SEQ ID NO: 110). :

30. The composition of matter of Claim 1 having the formula



30 and multimers thereof, wherein:

V^1 is a vehicle;

X^1 and X^2 are each independently selected from $-(L^1)_c-P^1$,

$-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

5 one or more of P^1 , P^2 , P^3 , and P^4 each independently comprise

Dz^2Lz^4 ;

L^1 , L^2 , L^3 , and L^4 are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

10 31. The composition of matter of Claim 30 of the formula

$P^1-(L^1)_c-P^2-(L^2)_d-V^1$.

32. The composition of matter of Claim 30 of the formula

$V^1-(L^1)_c-P^1-(L^2)_d-P^2$.

15 33. The composition of matter of Claim 30, wherein V^1 is an Fc domain.

34. The composition of matter of Claim 30 wherein V^1 is an IgG Fc domain.

35. The composition of matter of Claim 30 wherein V^1 is an IgG1 Fc domain.

20 36. The composition of matter of Claim 30 wherein V^1 comprises the sequence of SEQ ID NO: 2.

37. The composition of matter of Claim 30 wherein one or more of P^1 , P^2 , P^3 , and P^4 each independently comprises a sequence selected from:

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ. ID. NO: 100)

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ. ID. NO: 104)

25 $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ. ID. NO: 109)

$g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$ (SEQ ID NO: 101),
 $h^1h^2h^3CWh^6h^7WGh^{10}Ch^{12}h^{13}h^{14}$ (SEQ ID NO: 102), and
 $i^{12}i^3Ci^{5,6,7,8,9}i^{10}Ci^{12}i^{13}i^{14}$ (SEQ ID NO: 103)

wherein:

5 a^1, a^2, a^3 are each independently absent or amino acid residues;
 a^6 is an amino acid residue;
 a^9 is a basic or hydrophobic residue;
 a^8 is threonyl or isoleucyl;
 a^{12} is a neutral polar residue;

10 a^{13} and a^{14} are each independently absent or amino acid residues;
 b^1 and b^2 are each independently absent or amino acid residues;
 b^3 is an acidic or amide residue;
 b^5 is an amino acid residue;
 b^6 is an aromatic residue;

15 b^8 is an amino acid residue;
 b^{10} is T or I;
 b^{11} is a basic residue;
 b^{12} and b^{13} are each independently amino acid residues;
 b^{14} is a neutral polar residue;

20 b^{16}, b^{17} , and b^{18} are each independently absent or amino acid residues;
 c^1, c^2 , and c^3 are each independently absent or amino acid residues;
 c^5 is an amino acid residue;
 c^7 is an amino acid residue;
25 c^9 is T or I;
 c^{10} is a basic residue;
 c^{11} and c^{12} are each independently amino acid residues;
 c^{13} is a neutral polar residue;
 c^{14} is an amino acid residue;

30 c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and
 c^{18} is an amino acid residue or is absent;
 d^1 , d^2 , and d^3 are each independently absent or amino acid residues;
 d^5 , d^6 , and d^7 are each independently amino acid residues;
5 d^{10} is an amino acid residue;
 d^{12} is T or I;
 d^{13} is an amino acid residue; and
 d^{15} , d^{16} , and d^{17} are each independently absent or amino acid residues;

10 e^1 , e^2 , and e^3 are each independently absent or amino acid residues;
 e^5 , e^6 , e^7 , e^9 , and e^{13} are each independently amino acid residues;
 e^{11} is T or I; and
 e^{15} , e^{16} , and e^{17} are each independently absent or amino acid residues;
 f^1 , f^2 , and f^3 are absent or are amino acid residues;

15 f^5 is W, Y, or F;
 f^7 is an amino acid residue;
 f^9 is T or I;
 f^{10} is K, R, or H;
 f^{12} is C, a neutral polar residue, or a basic residue;

20 f^{13} is C, a neutral polar residue or is absent; and
 f^{14} is any amino acid residue or is absent;
provided that only one of f^1 , f^2 , and f^3 may be C, and only one of f^{12} ,
 f^{13} , and f^{14} may be C;

25 g^1 , g^2 and g^3 are each independently absent or amino acid residues;
 g^5 is a neutral polar residue;
 g^8 is a neutral polar residue;
 g^{10} is an acidic residue;
 g^{12} and g^{13} are each independently amino acid residues; and
 g^{14} is absent or is an amino acid residue;

30 h^1 , h^2 , and h^3 are each independently absent or amino acid residues;

h^6 is a hydrophobic residue;
 h^7 is a hydrophobic residue;
 h^{10} is an acidic or polar hydrophobic residue; and
 h^{12} , h^{13} , and h^{14} are each independently absent or amino acid residues;
5 i^1 is absent or is an amino acid residue;
 i^2 is a neutral polar residue;
 i^3 is an amino acid residue;
 i^5 , i^6 , i^7 , and i^8 are each independently amino acid residues;
 i^9 is an acidic residue;
10 i^{10} is an amino acid residue;
 i^{12} and i^{13} are each independently amino acid residues; and
 i^{14} is a neutral polar residue.

38. The composition of matter of claim 37, wherein:

a^9 is a basic residue.
15 b^3 is D, Q, or E;
 b^6 is W or Y;
 b^{11} is K or R; and
 b^{14} is V or L.
 c^{10} is K or R;
20 c^{13} is a I, L, or V;
 c^{17} is A or L;
 f^5 is W;
 f^7 is L; f^7 is K; and
 f^{10} is V.

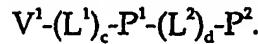
25 39. The composition of matter of Claim 37, wherein one or more of P^1 , P^2 , P^3 , and P^4 each independently comprises

$f^1f^2f^3KWDf^7Lf^8KQf^{12}f^{13}f^{14}$
(SEQ ID NO: 125).

40. The composition of matter of Claim 39 of the formula

30 $P^1-(L^1)_c-P^2-(L^2)_d-V^1$.

41. The composition of matter of Claim 39 of the formula



42. The composition of matter of Claim 39 having an amino acid sequence selected from SEQ ID NOS: 122, 123, and 124.

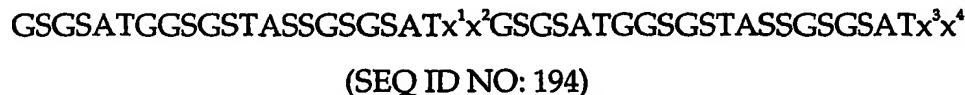
5 43. The composition of matter of Claim 40 wherein L^2 is greater than 5 amino acids.

44. The composition of matter of Claim 43 wherein L^2 is selected from



(SEQ ID NO: 193)

10 and



wherein x^1 and x^3 are each independently basic or hydrophobic residues and x^2 and x^4 are each independently hydrophobic residues.

15 45. The composition of matter of Claim 41 wherein L^2 is selected from

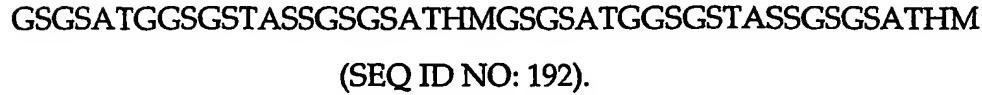


(SEQ ID NO: 59),



(SEQ ID NO: 190)

20 GSGSATGGSGSTASSGSGSATGS
(SEQ ID NO: 191), and



46. The composition of matter of Claim 28 comprising a sequence selected
25 from Table 2 (SEQ ID NOS: 29-39, 60-70, and 126-188).

47. The composition of matter of Claim 30 comprising a sequence selected
from Table 4 (SEQ ID NOS: 44-55).

48. The composition of matter of Claim 46, wherein V^1 is an Fc domain.

49. The composition of matter of Claim 46, wherein V^1 is an IgG Fc
30 domain.

50. The composition of matter of Claim 46, wherein V¹ is an IgG1 Fc domain.
51. A DNA encoding a composition of matter of Claim 34.
52. An expression vector comprising the DNA of Claim 51.
- 5 53. A host cell comprising the expression vector of Claim 52.
54. The cell of Claim 53, wherein the cell is an E. coli cell.
55. A method of treating a B-cell mediated autoimmune disease, which comprises administering a composition of matter of Claim 1.
56. A method of treating a B-cell mediated autoimmune disease, which 10 comprises administering a composition of matter of Claim 13.
57. A method of treating lupus, which comprises administering a composition of matter of Claim 1.
58. A method of treating lupus, which comprises administering a composition of matter of Claim 13.
- 15 59. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 1.
60. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 13.
61. A method of treating B-cell lymphoma, which comprises administering 20 a composition of matter of Claim 1.
62. A method of treating B-cell lymphoma, which comprises administering a composition of matter of Claim 13.

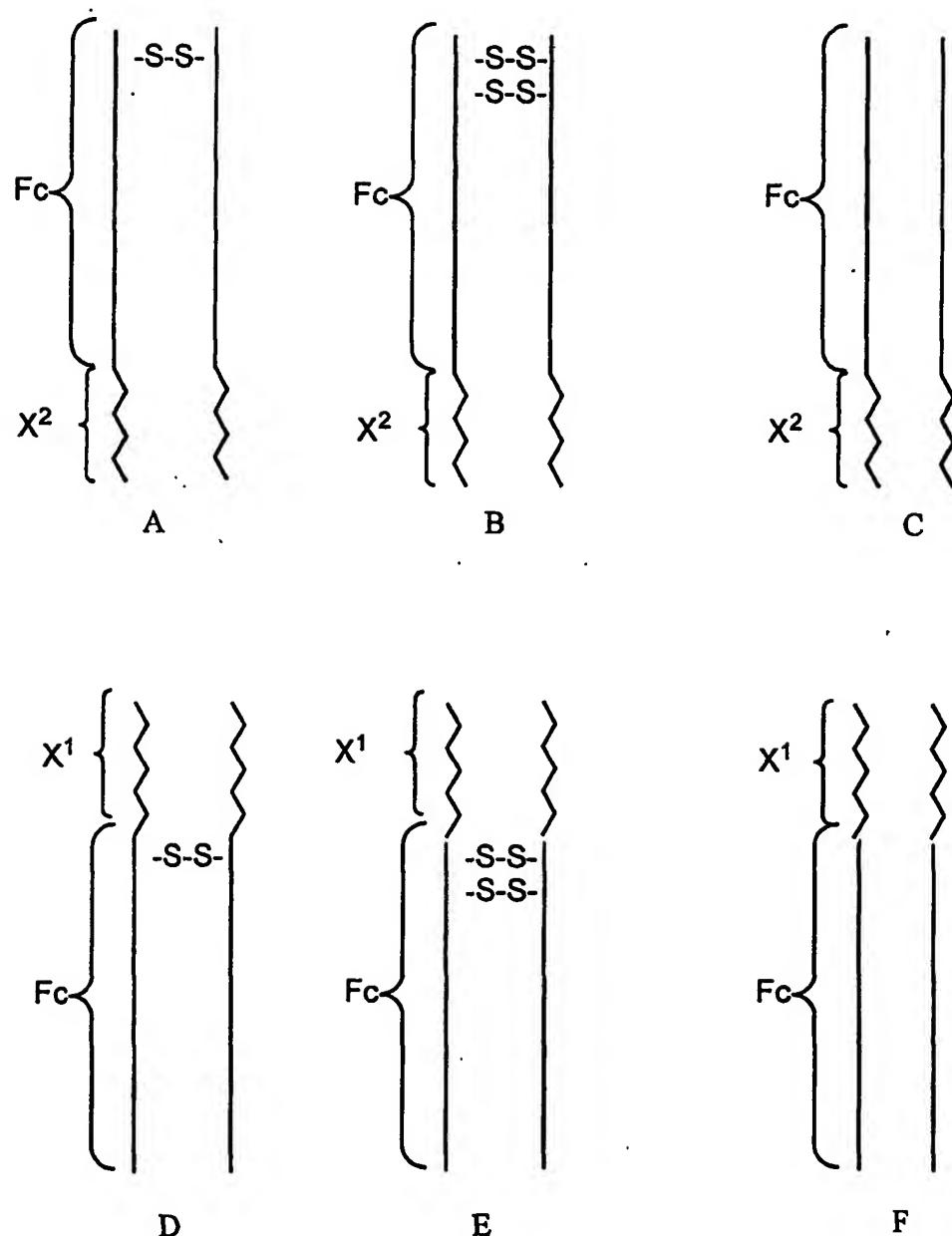
FIG. 1

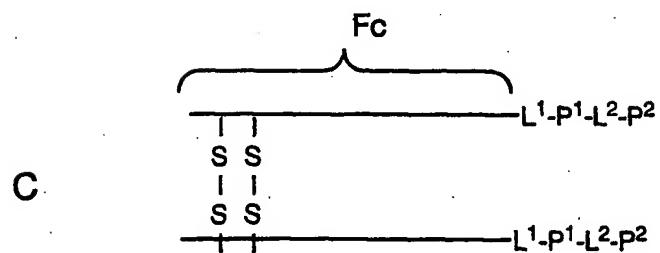
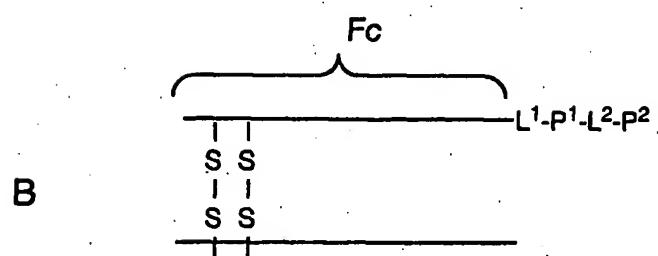
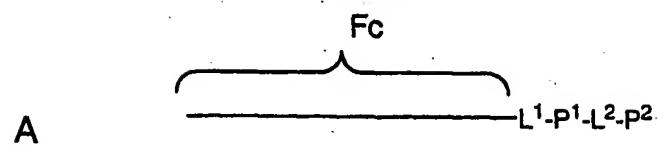
FIG. 2

FIG. 3

1 ATGGACAAA ACTCACACATGTCCACCTTGTCCAGCTCCGGAACTCCTGGGGGACCGTCA
 1 TACCTGTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGCAGT 60

a M D K T H T C P P C P A P E L L G G P S -
 61 GTCTTCTCTTCCCCC AAAACCCAAGGACACCCCTCATGATCTCCGGACCCCTGAGGTC
 61 CAGAAGGAGAAGGGGGTTTGGGTTCCGTGGAGTACTAGAGGGCCTGGGACTCCAG 120

a V F L F P P K P K D T L M I S R T P E V -
 121 ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTG
 121 TGTACGCACCACCCACCTGCACCTCGGTGCTCTGGGACTCCAGTTCAAGTTGACCATGCAC 180

a T C V V V D V S H E D P E V K F N W Y V -
 181 GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
 181 CTGCCGCACCTCCACGTATTACGGTTCTGTGTTCGGCCGCCCTCCTCGTCATGTTGTGTC 240

a D G V E V H N A K T K P R E E Q Y N S T -
 241 TACCGTGTGGTCAGCGTCCTCACCGCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
 241 ATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGCCTGACCGACTTACCGTTCTCATG 300

a Y R V V S V L T V L H Q D W L N G K E Y -
 301 AAGTGCAGGGCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCC
 301 TTCACGTTCCAGAGGTTGTTGGGAGGGTCGGGGTAGCTTTGGTAGAGGTTTCGG 360

a K C K V S N K A L P A P I E K T I S K A -
 361 AAAGGCAGCCCCGAGAACCAACAGGTGTACACCCCTGCCCATCCGGGATGAGCTGACC
 361 TTTCCCGTCGGGCCTTGGTCCACATGTGGACGGGGTAGGGCCCTACTCGACTGG 420

a K G Q P R E P Q V Y T L P P S R D E L T -
 421 AAGAACCAAGGTCAAGCCTGACCTGCTGGTCAAAGGCTCTATCCCAGCGACATGCCGTG
 421 TTCTGGTCCAGTCGGACTGGACGGACCAGTTCCGAAGATAGGGTCGCTGTAGCGGCAC 480

a K N Q V S L T C L V K G F Y P S D I A V -
 481 GAGTGGGAGAGCAATGGCAGCCGGAGAACAACTACAAGACCACGCCCTCCGTGCTGGAC
 481 CTCACCCCTCTCGTTACCGTCGGCCTCTTGTGATGTTCTGGTGGGAGGGCACGACCTG 540

a E W E S N G Q P E N N Y K T T P P V L D -
 541 TCCGACGGCTCCTCTTCCCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
 541 AGGCTGCCAGGAAGAAGGAGATGTCGTTGAGTGGCACCTGTTCTCGTCCACCGTCGTC 600

a S D G S F F L Y S K L T V D K S R W Q Q -
 601 GGGAACGTCTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAACTACACGCAGAAG
 601 CCCTTGAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTAGTGCCTTC 660

a G N V F S C S V M H E A L H N H Y T Q K -
 661 AGCCTCTCCCTGTCCTCGGGTAAA 684
 661 TCGGAGAGGGACAGAGGCCATT

a S L S L S P G K

FIG. 4A

1) AGP3-8-1-a

NdeI

|

TATGCCGGGTACTTGTTCGGCCGTTCCGTTGGGAATGCACTCACGCTGGTGGAGGCAGGT

1 -----+-----+-----+-----+-----+-----+-----+ 60

GCCCATGAACAAAGGGCAAGGGCACCCCTACGTGAGTGGGACCCCTCCGCCA

a M P G T C F P F P W E C T H A G G G G -

SalI

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

2) AGP3-8-2-a

NdeI

|

TATGTGGGGTGTGCTTGGCCGTTCCGTTGGGAATGTTCAAAGAAGGTGGAGGCAGGT

1 -----+-----+-----+-----+-----+-----+-----+ 60

ACACCCCCACGAACAAACCGGCAAGGGCACCCCTACAAAGTTCTTCCACCTCCGCCA

a M W G A C W P F P W E C F K E G G G G -

SalI

|

GGGG

61 ----- 69

CCCCAGCT

a G V D -

FIG. 4B

3) AGP3-8-4-a

NdeI |
 1 TATGGTTCCGTTCTGTGACCTGCTGACTAAACACTGTTCGAAGCTGGTGGAGGCGGT
 60 ACCAAGGCAAGACACTGGACGACTGATTGTGACAAAGCTTCGACCACCTCCGCCA

a M V P F C D L L T K H C F E A G G G G G -

SalI |
 61 GGGG
 69 CCCCAGCT

a G V D -

4) AGP3-12-4-a

November 6, 2000 12:53 ..

NdeI |
 1 TATGGTTCTCGTTGTAATACAAATGGGACGTTCTGACTAAACAGTGTTCACCAC
 60 ACCCAAGAGAACATTATGTTACCCCTGCAAGACTGATTGTCACAAAGGTGGTG

a M G S R C K Y K W D V L T K Q C F H H -

SalI |
 61 GGTGGAGGCGGTGGGG
 81 CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4C

5) AGP3-12-3-a

NdeI

TATGCTGCCGGGTTGTAATGGGACCTGCTGATCAAACAGTGGGTTGTGACCCGCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACGACGGCCAACATTTACCCCTGGACGACTAGTTGTCACCCAAACACTGGGCGAC

a M L P G C K W D L L I K Q W V C D P L -

SalI

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT

a G G G G G V D -

6) AGP3-12-5-a

NdeI

TATGTCTGCTGACTGTTACTTCGACATCCCTGACTAAATCTGACGTTGTACTTCTTCT

1 -----+-----+-----+-----+-----+ 60

ACAGACGACTGACAATGAAGCTGTAGGACTGATTAGACTGCAAACATGAAGAAGA

a M S A D C Y F D I L T K S D V C T S S -

SalI

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCAGCT

a G G G G G V D -

FIG. 4D

7) AGP3-12-8-a

NdeI

|

TATGTCTGACGACTGTATGTACGACCAGCTGACTCGTATGTTCATCTGTTCTAACCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAGACTGCTGACATACATGCTGGTCAGTGAGCATACAAGTAGACAAGATTGGAC

a M S D D C M Y D Q L T R M F I C S N L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-- 81

CCACCTCCGCCACCCAGCT

a G G G G V D -

8) AGP3-12-9-a

NdeI

|

TATGGACCTGAACTGTAAATACGACGAAC TGACTTACAAAGAATGGTGTCAAC

1 -----+-----+-----+-----+-----+-----+ 60

ACCTGGACTTGACATTTATGCTGCTTGACTGAATGTTCTTACACAGTCAAGTTG

a M D L N C K Y D E L T Y K E W C Q F N -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+-- 81

CCACCTCCGCCACCCAGCT

a G G G G V D -

FIG. 4E

9) AGP3-12-10-a

NdeI

|

TATGTTCCACGACTGTAAATACGACCTGCTGACTCGTCAGATGGTTGTCACGGTCTG

1 -----+-----+-----+-----+-----+-----+ 60

ACAAGGTGCTGACATTTATGCTGGACGACTGAGCAGTCTACCAAACAGTGCCAGAC

a M F H D C K Y D L L T R Q M V C H G L -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCCAGCT -

a G G G G G V D -

10) AGP3-12-11-a

NdeI

|

TATGCCGTAAACCACTGTTCTGGGACCACCTGCTGAAACAGGACATCTGTCCGTCTCCG

1 -----+-----+-----+-----+-----+-----+ 60

ACGCATTGGTGACAAAGACCCCTGGTGGACGACTTGTCCCTGTAGACAGGGCAGAGGC

a M R N H C F W D H L L K Q D I C P S P -

SalI

|

GGTGGAGGCGGTGGGG

61 -----+-----+ 81

CCACCTCCGCCACCCCAGCT

a G G G G G V D -

FIG. 4F

11) AGP3-12-14-a

|

NdeI

1 TATGGCTAACCGAGTGGTGGGACTCTCTGCTGAAAAAAAACGTTGTGAATTCTTC
 60 ACCGATTGGTCACAACCACCCCTGAGAGACGACTTTTTGCAAACACTTAAGAAG

a

M A N Q C W W D S L L K K N V C E F F -

SalI

61 GGTGGAGGCGGTGGGG
 81 CCACCTCCGCCACCCAGCT

a

G G G G G V D -

12) AGP3 Consensus

NdeI

1 TATGTTCCACGACTGCAAATGGGACCTGCTGACCAAAACAGTGGGTTGCCACGGTCTG
 60 gtATACAAGGTGCTGACGTTACCCCTGGACGACTGGTTGTCACCCAAACGGTGCCAGAC

a

M F H D C K W D L L T K Q W V C H G L -

SalI

61 GGTGGAGGCGGTGGGG
 81 CCACCTCCGCCACCCAGCT

a

G G G G G V D -

FIG. 5A

P
f
l
1
1
0
8
I

GATCAGCAGTCCCCGGAACATCGTAGCTGACGCCCTCGCGTTGCTCAGTTGCCAACCCC
1 60
CTAGTCGTCAGGGGCCCTGTAGCATCGACTGCCGAAGCGCAACGAGTCACACAGGTTGGGG
GGAAACGGGAAAAAGCAAGTTTCCCCGCTCCCGCGTTCAATAACTGAAAACCAACT
61 120
CCTTTGCCCTTTCGTTCAAAAGGGCGAGGGCCGAAAGTTATTGACTTTGGTATGA

B
G
I
I
I

ATTTCACAGTTAAATCACATTAACGACAGTAATCCCCGTTGATTGTGCCAACACA
121 180
TAAAGTGTCAAATTAGTGTAAATTGCTGTCATTAGGGCAACTAACACGCCGTTGTGT

-35

-10

----- Promoter (P_{copB}) ----->
GATCTTCGTCACAATTCTCAAGTCGCTGATTCAAAAAACTGTAGTATCCTCTGCAGAAC
181 240
CTAGAACAGTGTAAAGAGTTCAAGCGACTAAAGTTTGACATCATAGGAGACGCTTGT
|-->
mRNA start

GATCCCTGTTGAGTATTGAGGAGGGCGAGATGTCGCAGACAGAAAATGCAGTGACTCCCT
241 300
CTAGGGACAAACTCATAACTCCTCCGCTCTACAGCGCTGCTTTACGTCACTGAAGGA
M S Q T E N A V T S S -
--- copB protein --->

CATTGAGTCAAAAGCGGTTGCGCAGAGGTAAAGCCTATGACTGACTCTGAGAAACAAA
301 360
GTAACTCAGTTTCGCCAACACCGCTCTCCATTGGACTGACTGAGACTCTTGTTT
L S Q K R F V R R G K P M T D S E K Q M -

TGGCCGTTGCAAGAAAACGTCTTACACACAAAAGAGATAAAAGTTTGTCAAAATC
361 420
ACCGGCAACAAACGTTCTTGCAGAATGTGTGTTCTCTATTTCAAAACAGTTTAG
A V V A R K R L T H K E I K V F V K N P -

S
c
a
I

CTCTGAAGGATCTCATGGTTGAGTACTGCGAGAGAGAGGGATAACACAGGCTCAGTCG
421 480
GAGACTTCCCTAGAGTACCAACTCATGACGCTCTCTCCCTATTGTGTCCGAGTCAGC
L K D L M V E Y C E R E G I T Q A Q F V -

FIG. 5B

-35

----- Promoter (PrepA) ----->

| -- copB binding site -- |

481 TTGAGAAAATCATCAAAGATGAACTGCAAGACTGGATATACTAAAGTAAAGACTTTACT
AACTCTTTAGTAGTTCTACTTGACGTTCTGACCTATATGATTCAATTCTGAAATGA
c E K I I K D E L Q R L D I L K *

-10

541 TTGTGGCGTAGCATGCTAGATTACTGATCGTTAAGGAATTGTGGCTGGCACGCCGT
AACACCGCATCGTACGATCTAATGACTAGCAAATTCTAAAACACCGACCAGGTGCGCA
| -- mRNA -->

D
B r
m d
n I
I I

601 AAGGTGGCAAGGAACGGTTCTGATGTGGATTACAGGAGCCAGAAAAGCAAAACCCCG
TTCCACCCTTCCTGACCAAGACTACACCTAAATGTCCTCGGTCTTCTGTTGGGGC
c M W I Y R S Q K S K N P D -
--- copT (ORF) --->

<----- copA RNAI ----->

661 ATAATCTCTTCAACTTTGCGAGTACGAAAAGATTACCGGGGCCACTTAAACCGTATA
TATTAGAAGAAGTTGAAAACGCTCATGCTTCTAATGGCCCGGGTGAATTGGCATAT
c N L L Q L L R V R K D Y R G P L K P Y S -

----- Promoter (RNAI) ----->

-10 -35

<----- | ----->

721 GCCAACAAATTCACTGCGGGAGTATAGTTATATGCCCGAAAAGTTCAAGACTTCTT
CGGTTGTTAAGTCGATACGCCCTCATATCAATATACGGCCCTTCAAGTTCTGAAGAA
c Q Q F S Y A G S I V I C P E K F K T S F -

TCTGTGCTCGCTCCTCTGCGCATTGTAAGTGCAGGATGGTGTGACTGATCTCACCAA
781 AGACACGAGCGAGGAAGACGCGTAACATTACGTCTACCACACTGACTAGAAGTGGTTT
c C A R S F C A L * M T D L H Q T -
--- repA1 protein --->

D
r
a
I
I
I

841 CGTATTACCGCCAGGTAAAGAACCGAATCCGGTCTTACACCCCGTGAAGGTGCAGGAA
GCATAATGGCGGTCCATTCTTGGGCTTAGGCCACAAATGTGGGGACTTCCACGTCTT
c Y Y R Q V K N P N P V F T P R E G A G T -

901 CGCTGAAGTTCTGCGAAAAACTGATGGAAAAGCGGTGGCTTCACCTCCGTTTGATT
GCGACTTCAAGACGCTTTGACTACCTTCCGCCACCGAAGTGAAGGGCAAAACTAA
c L K F C E K L M E K A V G F T S R F D F -

FIG. 5C

B
S
t
B
I

TCGCCATTCAATGGCGCACGCCGTTCGCGTATCTGGCTGCCGTATGCCACCAGTGC
961 -----+-----+-----+-----+-----+-----+-----+-----+-----+-----+ 1020
AGCGGTAAGTACACCGCGTGCAGGGCAAGCGCACTAGACGCAGCGGATACGGTGGTCACG
c A I H V A H A R S R D L R R R M P P V L -

TGCGTCGTGGGCTATTGATGCGCTCTTGCAGGGCTGTGTTCCACTATGACCCGCTGG
1021 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1080
ACGCAGCAGCCGATAACTACCGAGAACGTCGGGACACAAAGGTGATACTGGGCGACC
c R R R A I D A L L Q G L C F H Y D P L A -

CCAACCGCGTCCAGTGCCTCCATCACCAACGCTGGCATTGAGTGCAGACTGGCAGGGAGT
1081 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1140
GGTTGGCGCAGGTACGAGGTAGTGGTGCACGGTAACTCACGCCCTGACCGCTGCCTCA
c N R V Q C S I T T L A I E C G L A T E S -

A
c
e
I
I
I

CTGCTGCCGGAAAATCTCCATCACCCGTGCCACCCGTGCCCTGACGTTCCCTGTCAGAGC
1141 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1200
GACGACGGCCCTTTGAGAGGTAGTGGGACGGTGGGACGGGACTGCAAGGACAGTCTCG
c A A G K L S I T R A T R A L T F L S E L -

TGGGACTGATTACCTACCAAGACGGAATATGACCCGTTATCGGGTGCCTACATTCCGACCG
1201 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1260
ACCTGACTAATGGATGGTCTGCCCTATAGCCACGATGTAAGGCTGGC
c G L I T Y Q T E Y D P L I G C Y I P T D -

ATATCACGTTACATCTGCACTGTTGCTGCCCTCGATGATCAGAGGAGGCAGTGGCCG
1261 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1320
TATAGTGCAGGTAGACGTGACAAACGACGGGAGCTACATAGTCTCCCTCCGTACCGGC
c I T F T S A L F A A L D V S E E A V A A -

CCCGCGCCGCCAGCCGTGGTATGGAAAACAAACAGCAAAAGCAGGGGCTGGATA
1321 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1380
GGCGCGCGCGTCGGCACACCATACCCCTTTGTTGCGTTTCTCGTCCCCGACCTAT
c A R R S R V V W E N K Q R K K Q G L D T -

CCCTGGGCATGGATGAACTGATAGCGAAAGCCTGGCGTTTGTGAGCGTTTCGCA
1381 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1440
GGGACCCGTACCTACTTGACTATCGCTTCGGACCGCAAAACAAGCACTCGCAAAAGCGT
c L G M D E L I A K A W R F V R E R F R S -

A
f
I
I
I

GTTATCAGACAGAGCTTAAGTCCCGTGAATAAGCGTGCCCGTGCAGCGTGTATGCGG
1441 -----+-----+-----+-----+-----+-----+-----+-----+-----+ 1500
CAATAGTCTGCTCGAATTCAAGGGCACCTTATTCGCACGGCACCGCAGCACTACGCC
c Y Q T E L K S R G I K R A R A R R D A D -

FIG. 5D

1501 ACAGGGAACGTCAGGATATTGTACCCCTGGTGAAACGGCAGCTGACGCCGAAATCGCGG 1560
 c TGTCCCTTGCGAGTCCCTATAACAGTGGGACCACTTGGCGCTGACTGCGCCTTAGCGCC
 R E R Q D I V T L V K R Q L T R E I A E -
 1561 AAGGGCGCTTCACTGCCAATCGTGAGGCGGAAAACCGAAGTTGAGCGTCGTGTGAAGG 1620
 c TTCCCGCGAAGTGCAGGTTAGCACTCCGCCATTGGCGCTCAACTCGCAGCACACTTCC
 G R F T A N R E A V K R E V E R R V K E -
 1621 AGCGCATGATTCTGTACGTAACCGTAATTACAGCCGGCTGGCCACAGCTTCCCCCTGAA 1680
 c TCGCGTACTAAAGACAGTGCATTGGCATTAAATGTCGGCCGACCGGTGTCGAAGGGGGACTT
 R M I L S R N R N Y S R L A T A S P *
 1681 AGTGACCTCCTCTGAATAATCCGCCCTGCGCCGGAGGCTTCCGCACGTCTGAAGCCCGAC 1740
 TCACTGGAGGGAGACTTATTAGGCCGGACGCCGCTCCGAAGGCGTGCAGACTTCGGGCTG

 P
 f
 l
 M
 I
 1741 AGCGCACAAAAATCAGCACACATACAAAAACAAACCTCATCATCCAGCTTCTGGTGCA 1800
 TCGCGTGTCTTGTGCTGGTGTATGTTTTGTTGGAGTAGTAGGTCGAAGGACACACGT
 1801 TCCGGCCCCCCTGTTTCGATACAAAACACGCCCTCACAGACGGGAATTTGCTTATCC 1860
 AGGCCGGGGGGGACAAAGCTATGTTGCGGAGTGTCTGCCCTAAAACGAATAGG

 |----- ori -----|
 1861 ACATTAACCGCAAGGGACTTCCCCATAAGGTTACAACCGTTCATGTCATAAAGGCCAT 1920
 TGTAATTGACGTTCCCTGAAGGGTATTCCAAATGTTGGCAAGTACAGTATTGCGGTA

 |----- ori -----|
 1921 CGCCAGCGTTACAGGGCAATGTATCTTAAACACCTGTTATATCTCCTTAAACT 1980
 GGCGGTCGAATGTCACGTTACATAGAAAATTGAGACAAATATAGAGGAAATTGGA

 |-----|
 1981 ACTTAATTACATTCAATTAAAAAGAAAACCTATTCACTGCCTGTCCTGGACAGACAGAT 2040
 TGAATTAATGTAAGTAAATTCTTCTTGGATAAGTGCAGGACAGGAACCTGTCGCTCA

 2041 ATGCACCTCCCACCGCAAGCGGGGGCCCTACCGGAGCCGCTTAGTTACAACACTCAG 2100
 a TACGTGGAGGGTGGCGTTGCCGCCGGGATGGCCTCGCGAAATCAATGTTGTGAGTC
 M H L P P Q A A G P Y R S R F S Y N T Q -
 --- repA4 protein ---> |----->

 2101 ACACAAACCACAGAAAAACCCCGGTCCAGCGCAGAACTGAAACACAAAGCCCTCCCTC 2160
 a TGTGTTGGTGGCTTTGGGCCAGGTGCGCTCTGACTTGGTGTTCGGGGAGGGAG
 T Q P P E K P R S S A E L K P Q S P S L -

 2161 ATAAACTGAAAAGCGGCCCCGCCCGGTCCGAAGGGCCGAAACAGAGTCGTTTAATTAT 2220
 a TATTGACTTTGCGCCGGGGCAGGCTCCCGCCTGTCAGCGAAAATTAATA
 I T E K R P R P G P K G R N R V A F N Y -

FIG. 5E

2221 GAATGTTGAACTACTTCATCATCGCTGTAGTCAGTCAGTCAGTCAGTACACG 2280
 a CTTACAACATTGATGAAGTAGTAGCGACAGTCAGAAGAGCGACCTCAAGAGTCATGTGC
 E C C N Y F I I A V S L L A G S S Q Y T -
 BS
 gf
 li
 II
 /
 2281 CTCGTAAGCGCCCTGACGGCCGCTAACGGAGATAACGCCCCGACTTCGGTAAACCC 2340
 a GAGCATTGCCGGACTGCCGGCGATTGCCCTCTATGCCGGCTGAAGGCCATTGGG
 L V S G P D G P L T R R Y A P T S G K P -
 TCGTCGGGACCACTCCGACCGCGCACAGAACGCTCTCATGGCTGAAAGCGGGTATGGTC 2400
 a AGCAGCCCTGGTGAGGCTGGCGCGTCTCGAGAGAGTACCGACTTCGCCATACCAAG
 S S G P L R P R T E A L S W L K A G M V -
 TGGCAGGGCTGGGATGGTAAGGTGAAATCTATCAATCAGTACCGGCTTACGCCGGC 2460
 2401 ACCGTCCCACCCCTACCCATTCACTTTAGATAGTTAGTCATGGCGAATGCCGGCGA
 a W Q G W G W V R *
 B
 s
 t
 E
 I
 I
 TCGCGGTTTACTCCTGTTCATATATGAAACAACAGGTACCGCCCTCCATGCCGCTG 2520
 2461 AGCCGCCAAATGAGGACAAAGTATATACTTGTGTCAGTGGCGGAAGGTACGGCGAC
 B
 S
 P
 L
 U
 I
 I
 I
 I
 ATGCGGCATATCCTGGTAACGATATCTGAATTGTTATACATGTGTATATACGTGGTAATG 2580
 2521 TACGCCGTATAGGACCATTGCTATAGACTTAACAATATGTACACATATATGCACCAATTAC
 ACAAAAATAGGACAAGTTAAAATTTACAGGGATGCAATGATTCAAACACGTAATCAAT 2640
 2581 TGTTTTATCCTGTTCAATTAAATGTCCGCTACGTTACTAAGTTGTGCATTAGTTA
 ATCGGGGGTGGCGAAGAACTCCAGCATGAGATCCCCGCGCTGGAGGATCATCCAGCCGG 2700
 2641 TAGCCCCCACCCGCTTGTGAGGTCGTACTCTAGGGCGCACCTCTAGTAGGTCGGCC
 CGTCCCGGAAACGATCCGAAGCCAACCTTCATAGAAGGCGGGTGGAAATCGAAAT 2760
 2701 GCAGGGCCTTGCTAAGGCTGGGTTGGAAAGTATCTCCGCCACCTAGCTTTA

FIG. 5F

| | | N | B |
|------|---|---|------|
| | | S | S |
| | | P | P |
| | | P | I |
| | | V | I |
| | CTCGTGATGGCAGGTTGGCGTCGCTGGTCGGTCATTCGAACCCCAGAGTCCGCTCA | | |
| 2761 | GAGCACTACCGTCCAACCCGCAAGCGAACAGCCAGTAAAGCTGGGGTCTCAGGGCGAGT | | 2820 |
| | GAAGAACTCGTCAAGAAGGCCATAGAAGGCCATGGCTGCCAATCGGGAGCGGCCATACC | | |
| 2821 | CTTCTTGAGCAGTTCTCCGCTATCTCCGCTACCGCACGCCCTAGCCCTGCCGCTATGG | | 2880 |
| f | * F F E D L L R Y F A I R Q S D P A A I G - | | |
| | <--- APHII protein [kanamycin resistance gene] --- | | |
| | GTAAAGCACGAGGAAGCGGTCAAGCCCATTGCCGCCAAGCTCTTCAGCAATATCACGGGT | | |
| 2881 | CATTCGTGCTCCTCGCCAGTCGGGTAAGCGGGGGTTCGAGAAGTCGTTATAGGCCA | | 2940 |
| f | Y L V L F R D A W E G G L E E A I D R T - | | |
| | AGCCAACGCTATGTCCTGATAGCGGTCCGCCACACCCAGGCCACAGTCGATGAATCC | | |
| 2941 | TCGGTTGCGATACAGGACTATGCCAGGCCGGTGTGGGTCGCCGGTGTCAAGCTACTTAGG | | 3000 |
| f | A L A I D Q Y R D A V G L R G C D I F G - | | |
| | AGAAAAGCGGCCATTTCCACCATGATATTGCCAAGCAGGCATGCCATGAGTCACGAC | | |
| 3001 | TCTTTTCGCCGGTAAAGGTGGTACTATAAGCCGTTGTCCTAGCGGTACTCAGTGTG | | 3060 |
| f | S F R G N E V M I N P L C A D G H T V V - | | |
| | GAGATCCTGCCGTGGCATGCCGCCCTGAGCCTGGCAACAGTCGGCTGGCGAG | | |
| 3061 | CTCTAGGAGCGGCCAGCCGTACGCCGGAACTCGGACCGCTTGTCAAGCCGACCGCGCTC | | 3120 |
| f | L D E G D P M R A K L R A F L E A P A L - | | |
| | CCCCTGATGCTCTCGTCCAGATCATCCTGATCGACAAGACCGGTTCCATCCGAGTACG | | |
| 3121 | GGGGACTACGAGAACGAGGTCTAGTAGGACTAGCTGTTGGCCGAAGGTAGGCTCATGC | | 3180 |
| f | G Q H E E D L D D Q D V L G A E M R T R - | | |
| | TGCTCGCTCGATGCGATGTTCGCTGGTGGTCAATGGCAGGTAGCCGGATCAAGCGT | | |
| 3181 | ACGAGCGAGCTACGCTACAAAGCAACCACAGCTACCCGCTCATCGGCTAGTCGCA | | 3240 |
| f | A R E I R H K A Q H D F P C T A P D L T - | | |
| | ATGCAGCCGCCATTGCATCAGCCATGATGGATACTTCTCGGCAGGAGCAAGGTGAGA | | |
| 3241 | TACGTCGGCGCGTAACGTAGTCGGTACTACCTATGAAAGAGCCGTCTCGTCACTCT | | 3300 |
| f | H L R R M A D A M I S V K E A P A L H S - | | |
| | TGACAGGAGATCCTGCCCGCACTTCGCCAATAGCAGCCAGTCCCTCCCGCTTCAGT | | |
| 3301 | ACTGTCCTCTAGGACGGGGCGTGAAGCGGGTTATCGTCGGTCAGGGAAAGGGCGAAGTC | | 3360 |
| f | S L L D Q G P V E G L L W D R G A E T - | | |
| | GACAACGTCGAGCACAGCTGCCAAGGAACGCCGTGAGCCAGCACGATAGCCGCGC | | |
| 3361 | CTGTTGAGCTCGTGTGACGCCGTTGCCAGCAGCACGGTCGGTCTATCGGCGCG | | 3420 |
| f | V V D L V A A C P V G T T A L W S L R A - | | |
| | TGCCTCGTCTGCAATTCAATTCAAGGACACCGGACAGGTCGGTCTTGACAAAAAGAACCGG | | |
| 3421 | ACGGAGCAGGACGTTAAGTAAGTCCTGTGGCCTGTCCAGCCAGAACGTGTTTCTGGCC | | 3480 |

FIG. 5G

f A E D Q L E N L V G S L D T K V F L V P -
 GCGCCCCTGCGCTGACAGCCGAAACACGGCGGATCAGAGCAGCCATTGTCGTTGTC
 3481 -----+-----+-----+-----+-----+-----+ 3540
 CGCGGGGACGCGACTGTCGGCTTGTGCCGCGTAGTCGTCGGCTAACAGACAACACG
 f R G Q A S L R F V A A D S C G I T Q Q A -
 E
 a
 g
 i
 CCAGTCATAGCCGAATAGCCTCTCCACCAAGCGGCCGGAGAACCTGCGTGCAATCCATC
 3541 -----+-----+-----+-----+-----+-----+ 3600
 GGTCAAGTATCGGCTTATCGGAGAGGTGGGTCGCCGCCCTTGGACGCACGTTAGGTAG
 f W D Y G F L R E V W A A P S G A H L G D -
 TTGTTCAATCATGCGAAACGATCCTCATCCTGTCTCTTGATCTGATCTTGATCCCCTGCG
 3601 -----+-----+-----+-----+-----+-----+ 3660
 AACAAAGTTAGTACGCTTGCTAGGAGTAGGACAGAGAACTAGACTAGAACTAGGGGACGC
 f Q E I M
 <-- APHII (kanamycin resistance) protein -->
 ----- mRNA APHII ----- | -----
 CCATCAGATCCTGGCGCAAGAAAGCCATCAGTTACTTGCAAGGGCTTCCAACCTT
 3661 -----+-----+-----+-----+-----+-----+ 3720
 GGTAGTCTAGGAACCGCCGTTCTTCGGTAGGTCAAATGAAACGTCGGAAAGGGTTGGAA
 -35

 <----- Promoter (APHII) -----
 ACCAGAGGGCGCCCCAGCTGGCAATTCCGGTTCGCTTGTCCATAAAACGCCAGTC
 3721 -----+-----+-----+-----+-----+-----+ 3780
 TGGTCTCCCGCGGGGTCGACCGTTAAGGCCAAGCGAACGACAGGTATTTGGCGGGTCAG
 TAGCTATGCCATGTAAGCCACTGCAAGTACCTGCTTCTCTTGCGCTTGCCTT
 3781 -----+-----+-----+-----+-----+-----+ 3840
 ATCGATAGCGGTACATTGGGTGACGTTGATGGACGAAAGAGAAACGCGAACGCAAAG
 CCTTGTCCAGATAGCCAGTAGCTGACATTCACTCCGGGTCAGCACCGTTCTGCGGACT
 3841 -----+-----+-----+-----+-----+-----+ 3900
 GGAACAGGTCTATCGGGTACGACTGTAAGTAGGCCCCAGTCGGCAAAGACGCCCTGA
 GGCTTCTACGTGTTCCGCTTCTTAGCAGCCCTTGCGCCCTGAGTGCCTGGCGAGCG
 3901 -----+-----+-----+-----+-----+-----+ 3960
 CCGAAAGATGCACAAGGGGAAGGAAATGTCGGAACGCCGGACTCACGAACGCCGTCGC
 | ----- par locus -----
 TGAAGCTACATATATGTGATCCGGCAAATCGCTGAATATTCCCTTGTCTCCGACCATC
 3961 -----+-----+-----+-----+-----+-----+ 4020
 ACTTCGATGTATACACTAGGCCGTTAGCGACTTATAAGGAAACAGAGGCTGGTAG
 B
 C
 g
 I
 ----- par locus -----
 AGGCACCTGAGTCGCTGCTTTTCGTGACATTCACTGTCGCTGCCACGGCTCTGGCA
 4021 -----+-----+-----+-----+-----+-----+ 4080
 TCCGTGGACTCAGCGACAGAAAAGCACTGTAAGTCAAGCGACGCCGAGACCGT
 ----- par locus -----

FIG. 5H

GTGAATGGGGTAAATGGCACTACAGGCGCCTTTATGGATTATGCAAGGAAACTACCC
 4081 -----+-----+-----+-----+-----+-----+-----+ 4140
 CACTTACCCCCATTACCGTATGTCGCGGAAAATACCTAAGTACGTTCTTGATGGG

----- par locus -----
 ATAATACAAGAAAAGCCGTACGGGCTCTCAGGGCTTATGGCGGGCTGCTATGT
 4141 -----+-----+-----+-----+-----+-----+-----+ 4200
 TATTATGTTCTTTCGGGCAGTCCCCGAAGAGTCCCAGAAATACCGCCCAGACGATACA

----- par locus -----
 GGTGCTATCTGACTTTGCTGTTCAGCAGTCCTGCCCTCTGATTTCCAGTCTGACCA
 4201 -----+-----+-----+-----+-----+-----+-----+ 4260
 CCACGATAGACTGAAAAACGACAAGTCGTCAAGGACGGGAGACTAAAAGGTCAAGACTGGT

----- par locus -----
 CTCGGATTATCCCGTACAGGTCAAGACTGGCTAATGCACCCAGTAAGGCAGCGGT
 4261 -----+-----+-----+-----+-----+-----+-----+ 4320
 GAAGCCTAATAGGGCACTGTCCAGTAAGTCTGACCGATTACGTGGTCATTCCGTGCCA

| | |
|---|---|
| N | B |
| S | s |
| i | a |
| | |
| I | I |

ATCATCAACAGGCTTACCCGTCTTACTGTCGAAGACGTGCGTAACGTATGCATGGCTC
 4321 -----+-----+-----+-----+-----+-----+-----+ 4380
 TAGTAGTTGTCGAATGGCAGAATGACAGCTTCTGCACGCATTGCATACGTACAGAGG

T1 hairpin
 -----> <---
 CCATGCGAGAGTAGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT
 4381 -----+-----+-----+-----+-----+-----+-----+ 4440
 GGTACGCTCTCATCCCTGACGGTCCGTAGTTATTTGCTTCCGAGTCAGCTTCTGA

|
 GGGCCTTCGTTTATCTGTTGTTGTCGGTAACGCTCTCCTGAGTAGGACAAATCCGC
 4441 -----+-----+-----+-----+-----+-----+-----+ 4500
 CCCGGAAAGCAAATAGACAACAAACAGCCACTGCGAGAGGACTCATCCTGTTAGGCG
 -- T1 stop --> |

| | |
|---|---|
| P | P |
| S | S |
| P | P |
| 1 | 1 |
| 4 | 4 |
| 0 | 0 |
| 6 | 6 |
| | |
| I | I |

CGGGAGCGGATTGAAACGTTGCGAACGAAACGGCCCGGAGGGTGGCGGGCAGGACGCCGC
 4501 -----+-----+-----+-----+-----+-----+-----+ 4560
 GCCCTCGCTAAACCTGCAACGCTTCGTTGCCGGCCCTCCACCGCCCGTCTGCGGGCG

T2 hairpin
 -----> <---
 CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTGCGT
 4561 -----+-----+-----+-----+-----+-----+-----+ 4620
 GTATTTGACGGTCCGTAGTTAATTGCTTCCGGTAGGACTGCCCTACCGAAAAACGCA
 ---- T2 stop ----> |

FIG. 5I

A
a
t
i
i

4621 TTCTACAAACTCTTGTTATTTCTAAATACATTCAAATATGGACGTCGTACTTAAC 4680
 AAGATGTTGAGAAAACAAATAAAAGATTATGTAAGTTATACCTGCAGCATGAATTG *

4681 TTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTAGAAATACTTGGCAGC 4740
 AAAATTCAACCGTTAGTTAACGAGGACAATTTAACGAAATCTTATGAAACCGTCG
 d S K F Y P C D I A G T L I A K S I S Q C -
 |<--- luxR protein ---

4741 GTTTGTGTTGAGTTTCATTGCGCATTGGTAAATGGAAAGTGACCGTGGCCTTAC 4800
 CCAAACAACTAACTCAAAGTAAACGCGTAACCAATTACCTTCACTGGCACCGAATG
 d R N T T N L K M Q A N T L H F T V T R K -

4801 TACAGCCTAATATTTGAAATATCCAAAGAGCTTTCCCTCGCATGCCACGCTAAC 4860
 ATGTCGGATTATAAAACTTTAGGGTCTCGAAAAGGAAGCGTACGGTGCATTG
 d S C G L I K S I D W S S K G E C A W A L -

4861 ATTCTTTCTCTTGGTAAATCGTTGTTGATTATTATTGCTATATTATTTTC 4920
 TAAGAAAAGAGAAAACCAATTAGCAACAAACTAAATAAAACGATATAAAATAAAAG
 d C E K E R K T L D N N S K N N A I N I K -

4921 GATAATTATCAACTAGAGAAGGAACAATTAGGTATGTCATACACGCATGAAAAATA 4980
 CTATTAATAGTTGATCTTCCTGTTAATTACCATACAAGTATGTCGTACATTTTAT
 d R Y N D V L S P V I L P I N M C A H L F -

B
s
m
i

4981 AACTATCTATATAGTTGCTTCTGAATGTGAAAACATAAGCATCCGAAGCCATTAT 5040
 TTGATAGATATATCAACAGAAAGAGACTTACACGTTTGATTGTAAGGCTTCGGTAATA
 d L S D I Y N D K E S H A F S L M G F G N -

5041 TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTCGCTCTTAA 5100
 ATCGTCATACTTATCCCTTGATTGGTCACTATTCTGGACTACTAAAGCGAAGAAATT
 d N A T H I P F S F G T I L G S S K A E K -

5101 TTACATTGGAGATTTTATTTACAGCATTGTTCAAATATATTCAAATTAATCGGTG 5160
 AATGTAAACCTCTAAAAAATAATGTCGTACAAAAGTTATATAAGGTTAATTAGCCAC
 d I V N P S K K N V A N N E F I N W N I P -

5161 AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTAAATTAGCGTCATCAT 5220
 TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTAAATCGCAGTAGTA
 d S H N S N S Y D V I P D Y K I L N A D D -

FIG. 5J

5221 AATATTGCCCTCATTTAGGGTAATTATCCAGAATTGAAATATCAGATTAAACCATAG 5280
 d TTATAACGGAGGTAAAAATCCCATTAAATAGGTCTTAACTTATAGTCTAAATTGGTATC
 Y Y Q R W K K P Y N D L I S I D S K V M -
 N
 r
 u
 I
 AATGAGGATAAAATGATCGCGAGTAAATAATATTACAAATGTACCAATTAGTCATATCAG 5281 5340
 TTACTCCTATTACTAGCGCTCATTATTATAAGTGTACATGGTAAATCAGTATAGTC
 S H P Y I I A L L Y Y E C H V M K T M D -
 ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTAATTATTAAATTATTCTGT 5341 5400
 TATTGTAACATTATAGTAATAACGAAGATGTCCGAAATTAAAATAATTAAAGACA
 S L C Q N I D N N S R C A K I K N I I R -
 AAGTGTCTCGGCATTATGTCTTCATACCCATCTCTTATCCTACCTATTGTTGTC 5401 5460
 TTACACAGCAGCCGTAACAGAAAGTATGGTAGAGAAATAGGAATGGATAACAAACAG
 Y T D D A N I D K M
 <---- luxR protein ---|
 GCAAGTTTGCCTATATATCATTAACGGTAATAGATTGACATTGATTCTAATAA 5461 5520
 CGTTCAAAACGCACAATATAGTAATTGGCATTATCTAACTGTAAACTAAGATTATT
 <----| <----| <----| <---- Promoter (luxPL) -----
 luxR mRNA start sites
 CRP Binding Site
 ATGGATTTGTCACACTATTATATCGCTGAAATACAATTGTTAACATAAGTACCTG 5521 5580
 TAACCTAAAAACAGTGTGATAATATAGCGAACATTATGTTAACAAATTGTATTGAC
 lux operator site -35 Promoter (luxPR) -10 C B
 TAGGATCGTACAGGTTACGCAAGAAAATGGTTGTTAGTCGATTAATCGATTGATT 5581 5640
 ATCCTAGCATGTCCAAATGCGTTTTACCAAAACATTCAGCTAATTAGCTAAACTAA
 |---- 1209-85 -----> |-- mRNA start -->
 NdeI
 CTAGATTTGTTTAACTAATTAAAGGAGGAATAACATATGATCGCTCCACCATGCACCAG 5641 5700
 GATCTAAACAAAATTGATTAATTCCCTCCTTATTGTATACTAGCGAGGTGGTACGTGGTC
 b M I A P P C T S -
 |-- RANK -->
 TGAGAACATTATGAGCATCTGGGACGGTGTGTAACAAATGTGAACCAGGAAAGTACAT 5701 5760
 ACTCTCGTAATACTCGTAGACCCCTGCCACGACATTGTTACACTGGTCCTTCATGTA
 b E K H Y E H L G R C C N K C E P G K Y M -

FIG. 5K

5761 GTCTTCTAAATGCACTACTACCTCTGACAGTGTATGTCGCCCTGTGGCCCGATGAATA 5820
 CAGAAGATTACGTGATGGAGACTGTCACATACAGACGGGACACCGGGCTACTTAT

b S S K C T T T S D S V C L P C G P D E Y -
 CTTGGATAGCTGGAATGAAGAAGATAAAATGCTTGCTGCATAAAAGTTGTGATACAGGCAA 5880
 5821 GAACCTATCGACCTTACTTCTTCTATTACGAACGACGTATTCAAACACTATGTCCGTT

b L D S W N E E D K C L L H K V C D T G K -
 ApaLI
 5881 GGCCTGGTGGCCGTGGTCGCCGGCAACAGTACGACCCCCCGGCGTGCACGGC 5940
 CCGGGACCACCGGCACCAGCGGCCGTGTCATGCTGGGGGCCGACGCGCACGTGCCG

b A L V A V V A G N S T T P R R C A C T A -
 KpnI
 Acc65I
 5941 TGGGTACCACTGGAGCCAGGACTGCGAGTGCTGCCGCCAACACCGAGTGCGGCCGGG 6000
 ACCCATGGTGACCTCGGTCTGACGCTCACGACGGCGGCGTTGTGGCTCACGCGCGCC

b G Y H W S Q D C E C C R R N T E C A P G -
 6001 CCTGGGCGCCAGCACCCGTTGCAGCTAACAAAGGACACAGTGTGAAACCTGCCCTGC 6060
 GGACCCGCGGGTGTGGCAACGTCGAGTTGTTCTGTGTCACACGTTGGAACGGAACG

b L G A Q H P L Q L N K D T V C K P C L A -
 6061 AGGCTACTTCTCTGATGCCCTTCCACGGACAAATGCAGACCCCTGGACCAACTGTAC 6120
 TCCGATGAAGAGACTACGGAAAAGGAGGTGCCTGTTACGTCTGGACCTGGTTGACATG

b G Y F S D A F S S T D K C R P W T N C T -
 6121 CTCCTTGAAAGAGAGTAGAACATCATGGACAGAGAAATCCGATGTGGTTGCAGTTC 6180
 GAAGGAACCTTCTCATCTTGTAGTACCCGTCTCTTAGGCTACACCAAACGTCAAG

b F L G K R V E H H G T E K S D V V C S S -
 AccI
 SalI
 6181 TTCTCTGCCAGCTAGAAAACCACCAAATGAACCCATGTTACGTGACAAAACAC 6240
 AAGAGACGGTCGATCTTGGTGGTTACTGGGTACAAATGCAGCTGTTGAGTGTG

b S L P A R K P P N E P H V Y V D K T H T -
 <-- end RANK --||--start Fc-->

FIG. 5L

BspEI
6241 ATGTCCACCTTGTCCAGCTCCGGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC 6300
TACAGGTGGAACAGGTGCGAGGCCTTGAGGACCCCCCTGGCAGTCAGAAGGAGAACGGGGG
b C P P C P A P E L L G G P S V F L F P P -
BspHI
6301 AAAACCCAAGGACACCCCTCATGATCTCCGGACCCCTGAGGTACATGCGTGGTGGTGG 6360
TTTGGGTTCTGTGGGAGTACTAGAGGGCTGGGACTCCAGTGTACCGCACCAACCT
b K P K D T L M I S R T P E V T C V V V D -
CGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA 6420
6361 GCACTCGGTGCTCTGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCACCTCCACGT
b V S H E D P E V K F N W Y V D G V E V H -
TAATGCCAAGACAAAGCCGGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGT 6480
6421 ATTACGGTTCTGTTCGGCGCCCTCCTCGTCATGTTGTCGTGCATGGCACACCAGTCGCA
b N A K T K P R E E Q Y N S T Y R V V S V -
EcoNI
6481 CCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCAA 6540
GGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCTCATGTTCACGTTCCAGAGGTT
b L T V L H Q D W L N G K E Y K C K V S N -
CAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA 6600
6541 GTTTCGGGAGGGTCGGGGTAGCTCTTGGTAGAGGTTCGGTTCCCGTCGGGCTCT
b K A L P A P I E K T I S K A K G Q P R E -
BsrGI
6601 ACCACAGGTGTACACCCCTGCCCTATCCGGGATGAGCTGACCAAGAACAGGTCAAGCCT 6660
TGGTGTCCACATGTGGACGGGGTAGGGCCCTACTCGACTGGTTCTGGTCCAGTCGGA
b P Q V Y T L P P S R D E L T K N Q V S L -
GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATGCCGTGGAGTGGAGAGCAATGG 6720
6661 CTGGACGGACCAGTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCCCTCTCGTTACC
b T C L V K G F Y P S D I A V E W E S N G -
GCAGCCGGAGAACAACTACAAGACCAACGCCCTCCGTGCTGGACTCCGACGGCTCCCTCTT 6780
6721 CGTCGGCCTCTTGTGATGTTCTGGTGGAGGGCACCTGAGGCTGCCGAGGAAGAA

FIG. 5M

b Q P E N N Y K T T P P V L D S D G S F F -
 6781 CCTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTCTCATG
 6840 GGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGAGAAAGAGTAC

b L Y S K L T V D K S R W Q Q G N V F S C -
 6841 CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC
 6900 GAGGCACGTACTCCGAGACGTGTTGGTATGTCGCTCTCGGAGAGGGACAGAGG

b S V M H E A L H N H Y T Q K S L S L S P -
 6901 GGGTAAATAATGGATCCCGGAAAGAAGAAGAAGAAGAAGAAGAAGCCCAGAAAGGAAGCTGA
 6960 CCCATTATACCTAGGCCCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTCGACT

b G K *
 6961 BlpI |
 7020 GTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAACCCCTTGGGGCTCTAAACGGGT
 CAACCGACGACGGTGGCAGTCGTTATTGATCGTATTGGGGAACCCCGGAGATTGCCA
 7080 CTTGAGGGGTTTTGCTGAAAGGAGGAACCGCTTTCACGCTTTCACGCGATAAATA
 GAACTCCCCAAAAAACGACTTCCCTGGCAGAAGTGCAGAAGTGCCTATTAT
 -T7 stop --->|

T7 hairpin
 -----> <-----
 ----->

7081 AGTAACGATCCGGTCCAGTAATGACCTCAGAACTCCATCTGGATTGTTCAGAACGCTCG
 7140 TCATTGCTAGGCCAGGTCAATTACTGGAGTCTTGAGGTAGACCTAACAGTCCTGCGAGC
 toop hairpin
 ----->
 7141 GTTGCCGCCGGCGTTTTATTGGTGGAGAACGCAACTTGTGCGCCAATCGAGCC
 CAACGGCGCCCGCAAAAATAACCACTCTTACGGTGGTGAACAGCGCGGTAGCTCGG
 -- toop stop -->|

7201 ATGTCGTCGTCACGACCCCCCATTCAAGAACAGCAAGCAGCATTGAGAACATTGGAATC
 7260 TACAGCAGCAGTTGCTGGGGGTAAGTTCTGTCGTTCTCGTAACCTTGAAACCTTAG

7261 CAGTCCCTCTTCCACCTGCTGACCG
 7285 GTCAGGGAGAAGGTGGACGTGGC

FIG. 6A

(AatII sticky end)
(position #4358 in pAMG21)

| | |
|--|-------------------------------|
| 5' | GCCTAACGTATGCATGGTCTCC- |
| 3' | TGCACGCATTGCATAACGTACCAAGAGG- |
| -CCATGCGAGAGTAGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT- | |
| -GGTACGCTCTCATCCCTGACGGTCCGTAGTTATTGCTTCGAGTCAGCTTCTGA- | |
| -GGGCCTTCGTTTATCTGTTGTCGGTGAACGCTCCTGAGTAGGACAAATCCGC- | |
| -CCCGAAAGCAAATAGACAAACAGCCACTTGCAGAGGACTCATCCTGTTAGGCG- | |
| -CGGGAGCGGATTGAACTGCGAAGCAACGGCCGGAGGGTGGCGGGCAGGACGCCGC- | |
| -GCCCTCGCCTAAACTGCAACGCTTCGTTGCCGGCTCCCACGCCGTCCGTGCGGGCG- | |
| -CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCGTACGGATGGCCTTTGCGT- | |
| -GTATTGACGGTCCGTAGTTAATTGCTTCGGTAGGACTGCCTACCGGAAAAACGCA- | |
| AatII | |
| -TTCTACAAACTCTTTGTTATTTTCTAAATACATCAAATATGGACGTCGTACTTAAC- | |
| -AAGATGTTGAGAAAACAATAAAAGATTATGTAAGTTATACCTGCAGCATGAATTG- | |
| -TTTAAAGTATGGCAATCAATTGCTCCTGTTAAATTGCTTTAGAAATACTTTGGCAGC- | |
| -AAAATTTCATACCGTTAGTTAACGAGGACAATTAAACGAAATTTATGAAACCGTCG- | |
| -GGTTGTTGATGAGTTCAATTGCGCATTGGTTAAATGAAAGTGACCGTGCCTTAC- | |
| -CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTACCTTACTGGCACGCAATG- | |
| -TACAGCCTAATATTTTGAATATCCCAAGAGCTTTTCCCTCGCATGCCACGCTAAAC- | |
| -ATGTCGGATTATAAAAACCTTATAGGGTCTCGAAAAAGGAAGCGTACGGGTGCGATTG- | |
| -ATTCTTTCTCTTTGGTAAATCGTTGTTGATTATTATTTGCTATATTATTTTC- | |
| -TAAGAAAAGAGAAAACCAATTAGCAACAAACTAAATAAAACGATATAAATAAAAAG- | |
| -GATAATTATCAACTAGAGAAGGAACAATTAAATGGTATGTTACACGCATGTAAAAATA- | |
| -CTATTAATAGTTGATCTCTTGTAAATTACCATACAAGTATGCGTACATTTTAT- | |
| -AACTATCTATATAGTTGCTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGGCCATTAT- | |
| -TTGATAGATATCAACAGAAAGAGACTTACACGTTGATTGTAAGGCTTCGTAATA- | |
| -TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTCGCTTAA- | |
| -ATCGTCATACTTATCCCTTGATTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT- | |
| -TTACATTGGAGATTTTATTTACAGCATTGTTCAAATATATTCAATTAACTCGGTG- | |
| -AATGAAACCTCTAAAAAATTCGTAACAAAGTTATATAAGGTTATTAGCCAC- | |
| -AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTAAATTAGCGTCATCAT- | |
| -TTACTAACCTCAATCTTATTAGATGATACCTAGTATAAAATAATTAAATCGCAGTAGTA- | |
| -AATATTGCCCTCATTAGGGTAATTATCCAGAATTGAAATATCAGATTAAACCATAG- | |
| -TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACCTTATAGTCTAAATTGGTATC- | |
| -AATGAGGATAATGATCGCGAGTAAATAATATTCAACATGTACCAATTAGTCATATCAG- | |
| -TTACTCCTATTACTAGCGCTCATTATATAAGTGTACATGGTAAATCAGTATAGTC- | |
| -ATAAGCATTGATAATATCATTATTGCTCTACAGGCTTAAATTATTAATTATCTGT- | |
| -TATTGCTTAACATTAGTAAACGAAGATGTCGAAATTAAATAAGACA- | |
| -AAGTGTGCGCGCATTTATGCTTTCATACCCATCTTTATCCTTACCTATTGTTGTC- | |
| -TTCACAGCAGCGTAAATACAGAAAGTATGGTAGAGAAAATAGGAATGGATAACAAACAG- | |
| -GCAAGTTTGCGTGTATATATCATTAAACGGTAATAGATTGACATTGATTCTAAATAA- | |
| -CGTTCAAAACGCACAATATATAGTAAATTGCCATTCTAATGCTAAACTAAGATTATT- | |

FIG. 6B

-ATTGGATTTGTCACACTATTATATCGCTTGAATACAATTGTTAACATAAGTACCTG-
-TAACCTAAAACAGTGTGATAATATAGCGAACCTTATGTTAACAAATTGTATTGAC-
-TAGGATCGTACAGGTTACGCAAGAAAATGGTTGTTAGTCGATTAATCGATTTGATT-
-ATCCTAGCATGTCCTAACATGCGTTCTTACCAAACAATATCAGCTAATTAGCTAACTAA-
-CTAGATTGTTAACTAATTAAAGGAGGAATAACATATGGTTAACCGTTGGAATTGCA-
-GATCTAAACAAAATTGATTAATTCTCCTTATTGTATACCAATTGCGAACCTTAAGCT-

SacII.

-GCTCACTAGTGTGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGAAAGAA-
-CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTCTT-
-GAAGAAGAAGAAGAAAGCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
-CTTCTTCTTCTTCTGGGCTTCCTCGACTCAACCGACGACGGTGGCGACTCGTTAT-
-ACTAGCATAACCCCTTGGGGCCTCTAACGGGTCTGAGGGTTTTGCTGAAAGGAGG-
-TGATCGTATTGGGAACCCGGAGATTGCCAGAACTCCCCAAAAACGACTTCCCTCC-
-AACCGCTCTCACGCTTCAACGC 3' [SacII sticky end]
-TTGGCGAGAAGTGCAGAAGTG 5' (position #5904 in pAMG21)

FIG. 7

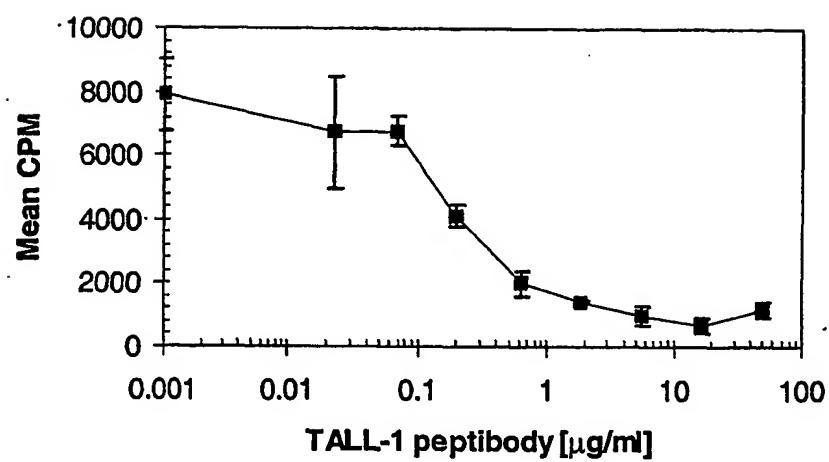


FIG. 8

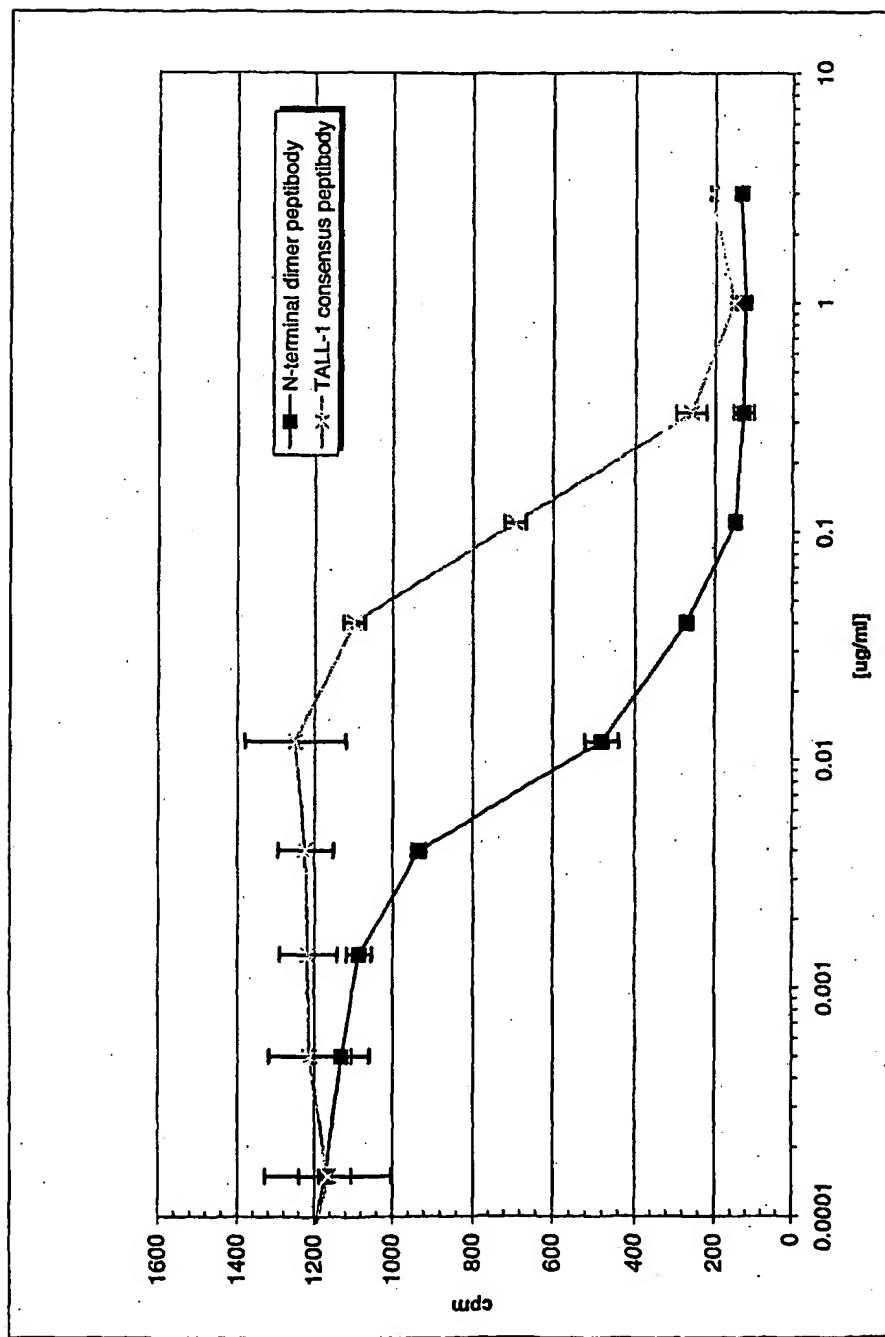


FIG. 9

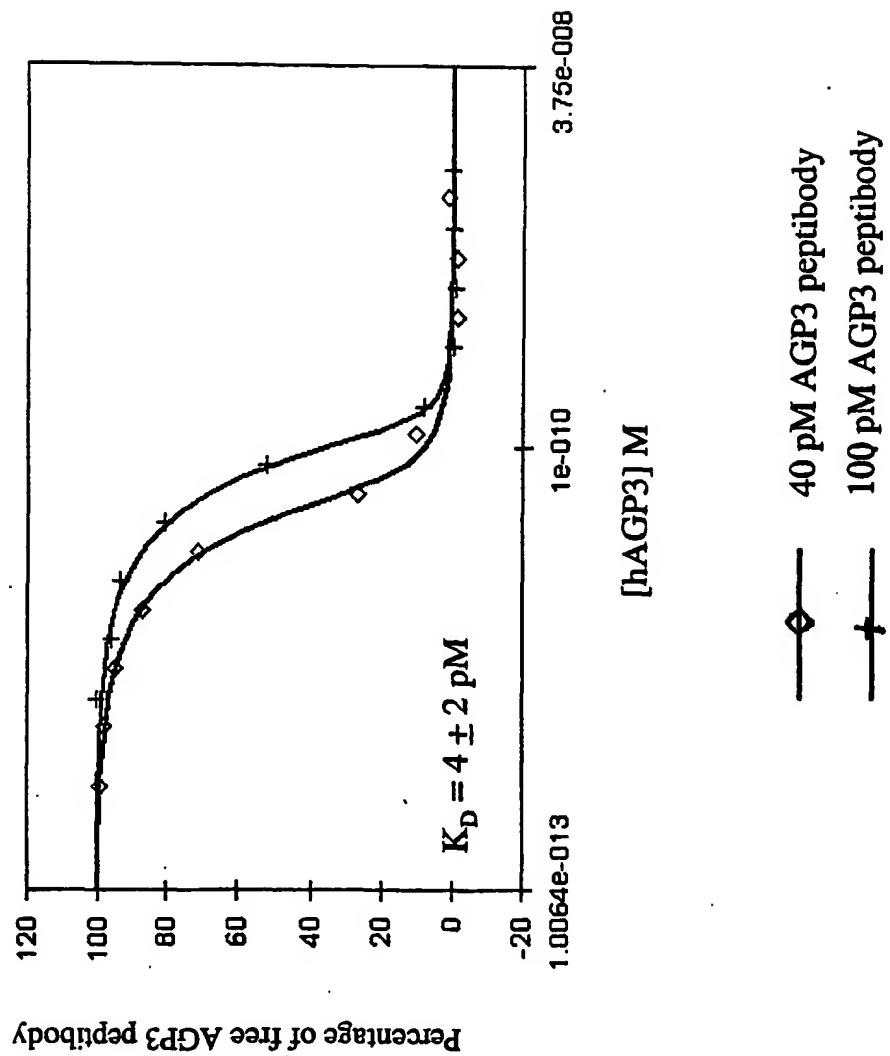


FIG. 10A

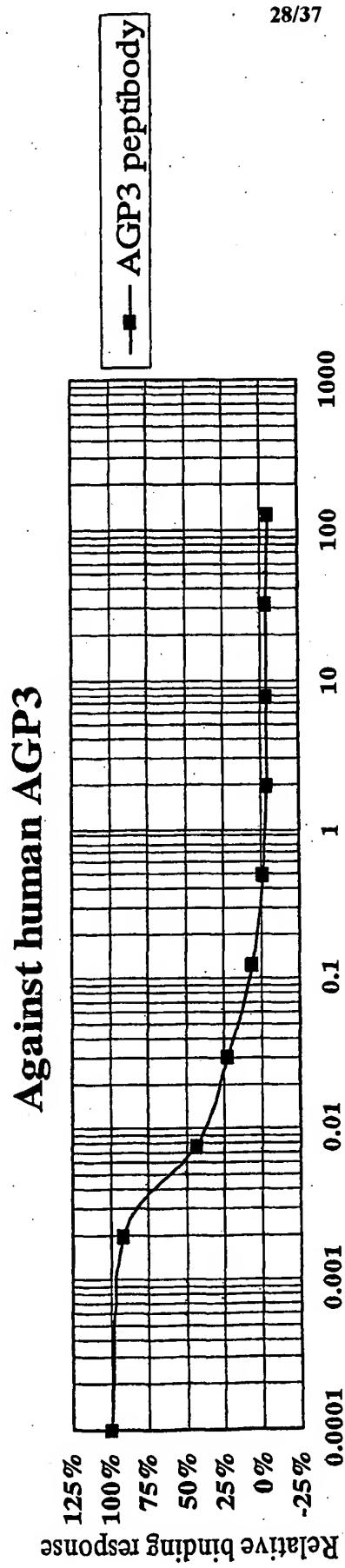


FIG. 10B

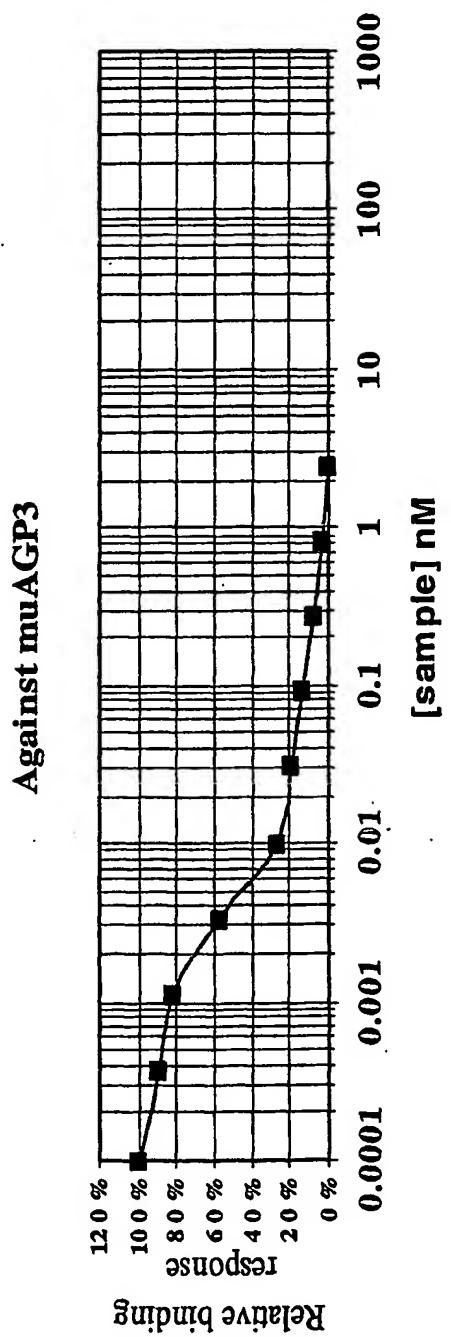


FIG. 11A

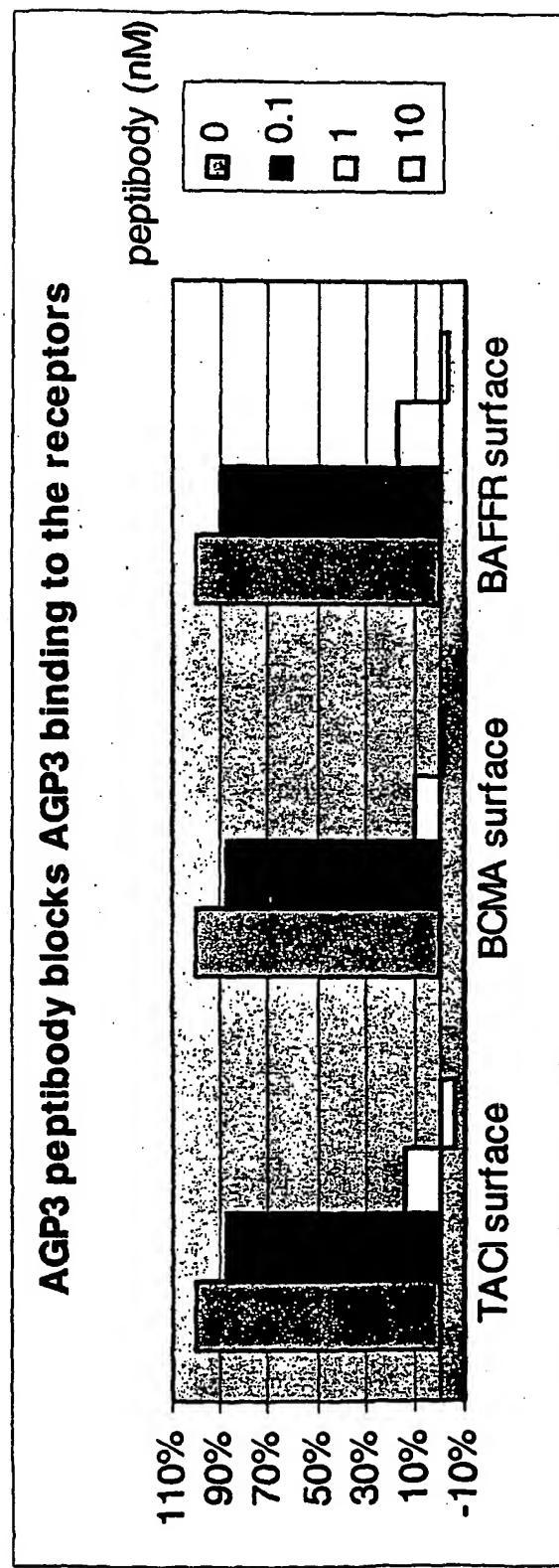


FIG. 11B

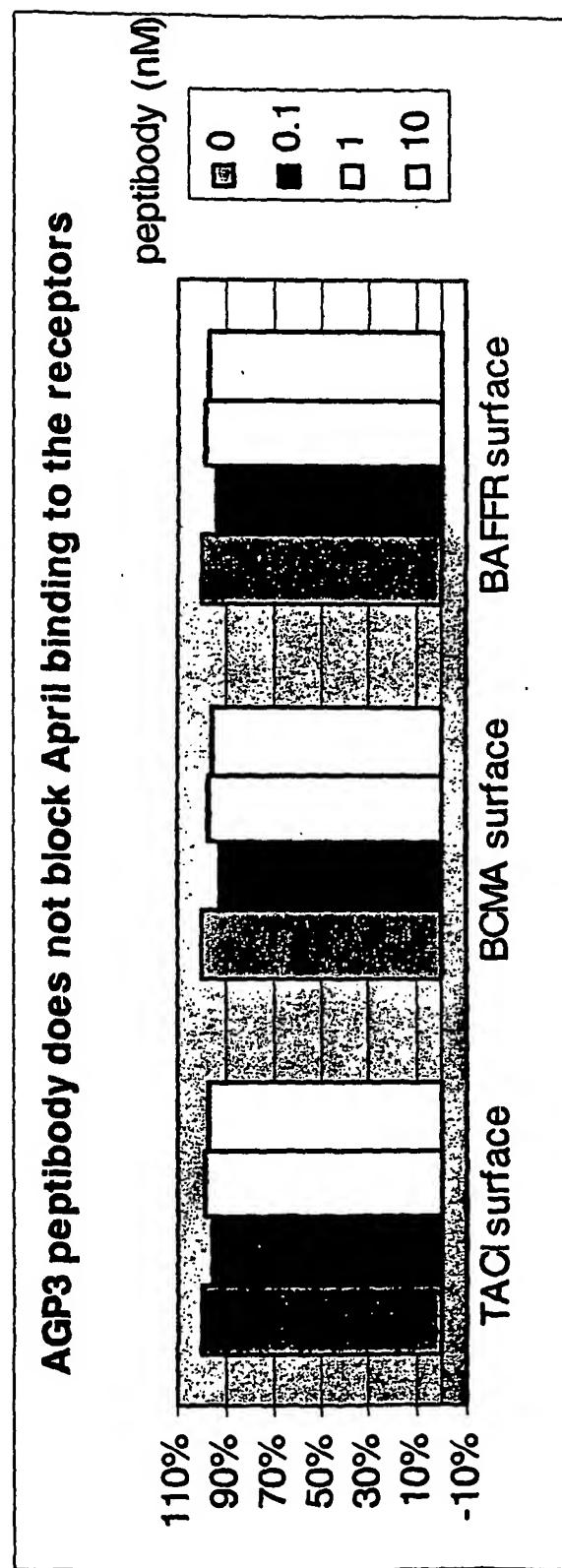


FIG. 12A

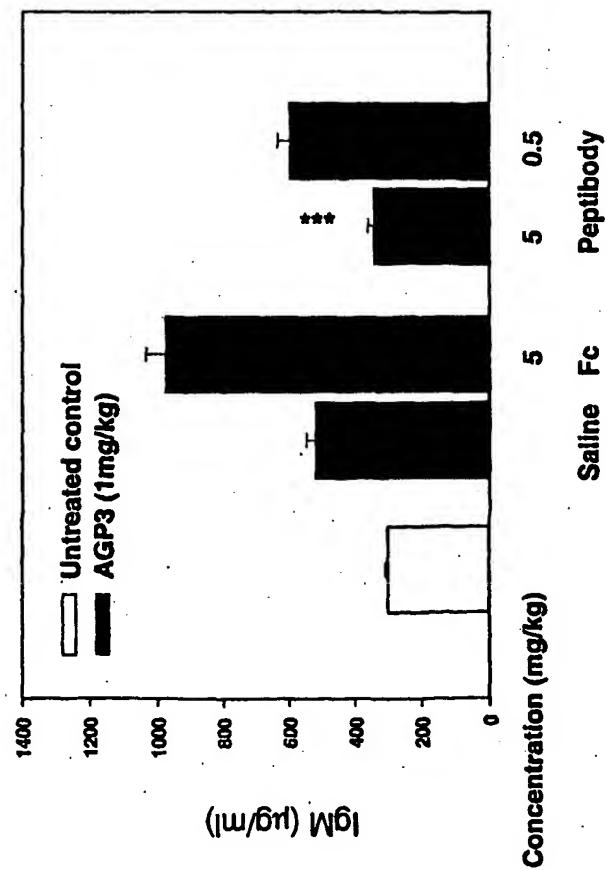


FIG. 12B

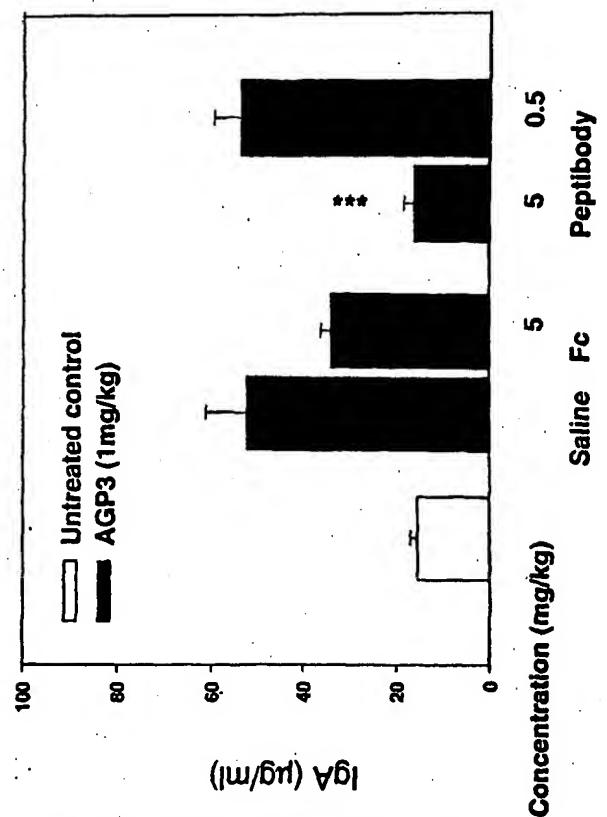


FIG. 13

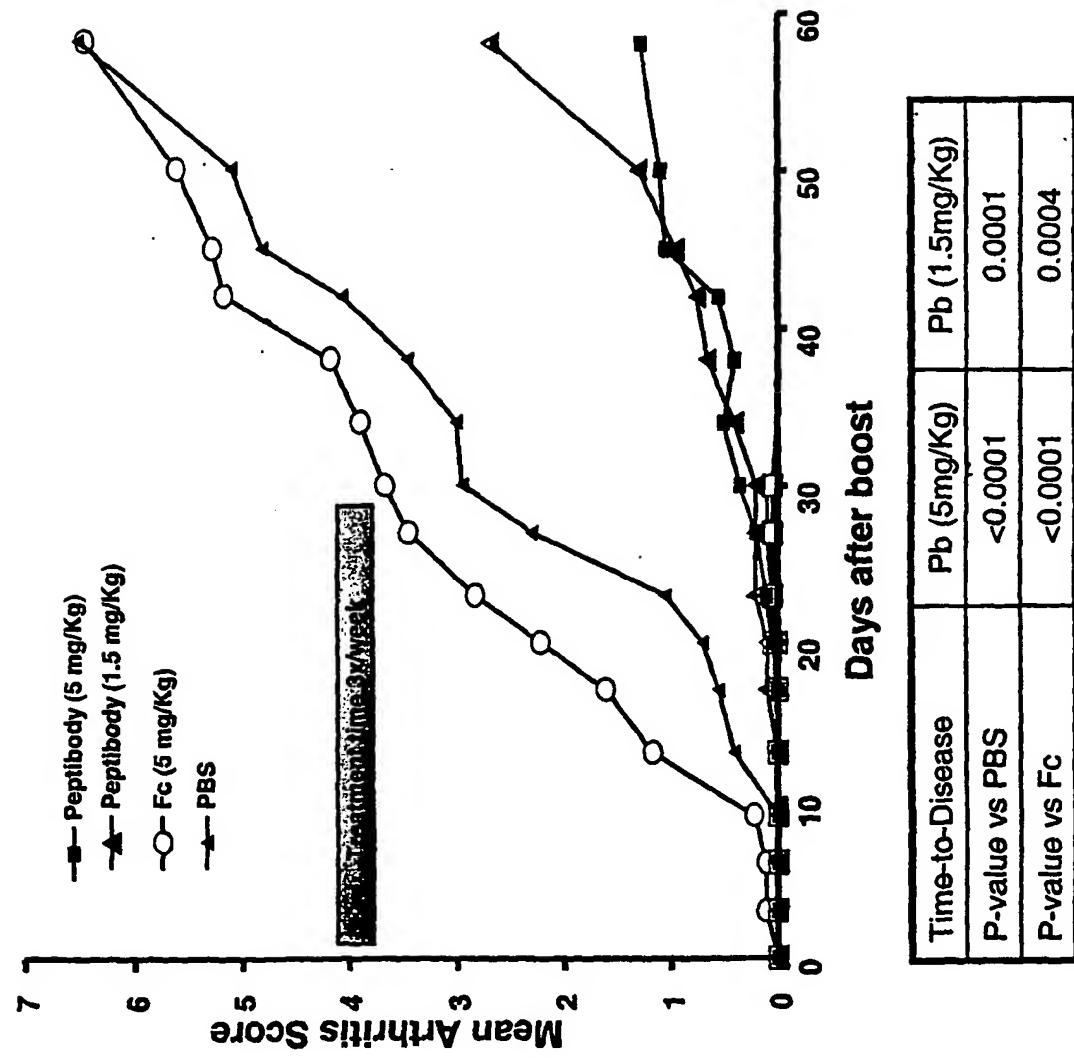
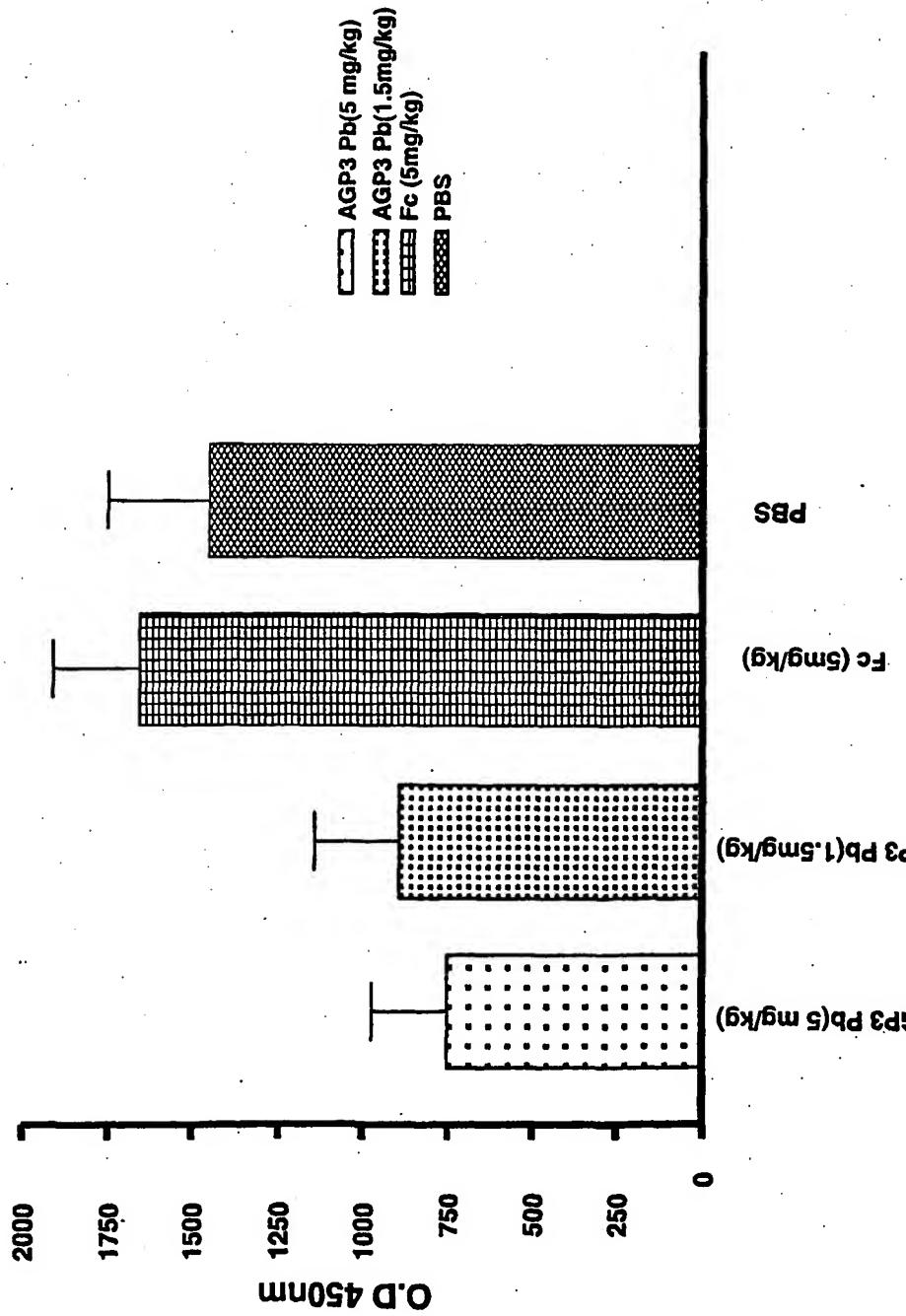


FIG. 14

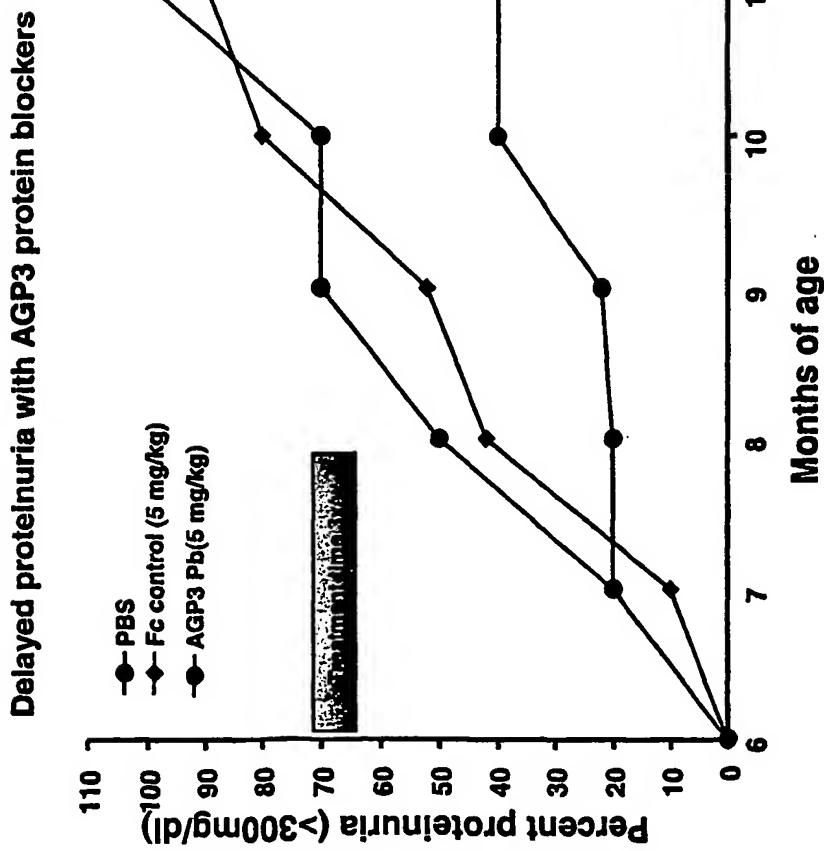
**Reduced anti-collagen IgG2b upon
treatment with AGP3 peptibody**



Serum samples were taken one week after final treatment of reagent (day 35).

The graph above is representative of the IgG1, IgG3, and IgG2a isotypes as well.

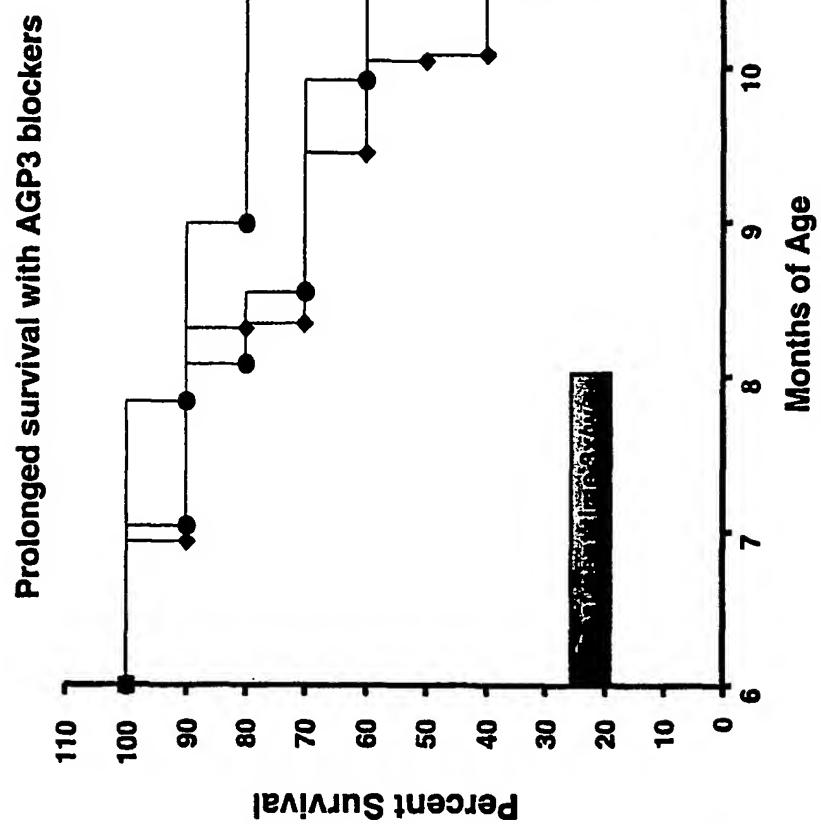
Fig. 15A



| Proteinuria Incidence | Pb |
|-----------------------|--------|
| p-value vs PBS | 0.0108 |
| P-vs Fc | 0.0573 |

P-value based Fisher's Exact test

Fig. 15B



| Time-to-Death | Pb |
|----------------|--------|
| p-value vs PBS | 0.3685 |
| p-value vs Fc | 0.0159 |

P-value based log-rank test

FIG. 16A

BamHI

1 ATGCTTCCAGGCTGCAAGTGGATCTTCTTATTAAGCAATGGGTATGCGATCCACTTGGA 60
 1 TACGAAGGTCCGACGTCACCCCTAGAAGAATAATTGTTACCCATACGCTAGGTGAACCT

M L P G C K W D L L I K Q W V C D P L G -

61 TCCGGTTCTGCTACTGGTGGTCCGGCTCCACCGCAAGCTCTGGTTCAGGCAGTGCAGACT 120
 61 AGGCCAAGACGATGACCACCAAGGCCGAGGTGGCGTTGAGACCAAGTCCGTACGCTGA

S G S A T G G S G S T A S S S G S G S A T -

NdeI

121 CATATGCTGCCGGGTTGTAATGGGACCTGCTGATCAAACAGTGGGTTGTGACCCGCTG 180
 121 GTATACGACGGCCAACATTTACCTGGACGACTAGTTGTCACCCAAACACTGGCGAC

H M L P G C K W D L L I K Q W V C D P L -

SalI

181 GGTGGAGGCCGGTGGGTCGACAAAACTCACACATGTCCACCTTGTCCAGCTCCGAACTC 240
 181 CCACCTCCGCCACCCAGCTGTTGAGTGTACAGGTGGAACAGGTGAGGCCCTTGAG

G G G G G V D K T H T C P P C P A P E L -

241 CTGGGGGACCGTCAGTCTTCTCTTCCCCAAAACCCAAGGACACCCCTCATGATCTCC 300
 241 GACCCCCCTGGCAGTCAGAAGGAGAAGGGGGTTTGGGCTGTGGAGTACTAGAGG

L G G P S V F L F P P K P K D T L M I S -

301 CGGACCCCTGAGGTACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAG 360
 301 GCCTGGGACTCCAGTGTACGCACCACCCACTGCACTCGGTGTCTGGACTCCAGTTC

R T P E V T C V V V D V S H E D P E V K -

361 TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGGGAGGAG 420
 361 AAGTTGACCATGCACCTGCCACCTCCACGTATTACGGTTCTGTTGGCCTCCCTC

F N W Y V D G V E V H N A K T K P R E E -

421 CAGTACAACAGCACGTACCGTGTGGTCAGCGCCTCACCGCCTGCACCAGGACTGGCTG 480
 421 GTCATGTTGTCGTGCATGGCACACCAAGTCGCAGGAGTGGCAGGACGTGGCCTGACCGAC

Q Y N S T Y R V V S V L T V L H Q D W L -

FIG. 16B

AATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGCCCTCCCAGCCCCATCGAGAAA
 481 -----+-----+-----+-----+-----+-----+ 540
 TTACCGTCTCATGTTCACGTTCCAGAGGTTGTTGGGAGGGTCGGGGTAGCTCTTT
 N G K E Y K C K V S N K A L P A P I E K -
 ACCATCTCCAAAGCAAAGGGCAGCCCCGAGAACACAGGTGTACACCCTGCCCATCC
 541 -----+-----+-----+-----+-----+-----+ 600
 TGGTAGAGGTTTCGGTTCCGTCGGGCTTGGTGTCCACATGGGGACGGGGTAGG
 T I S K A K G Q P R E P Q V Y T L P P S -
 CGGGATGAGCTGACCAAAGAACCAAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC
 601 -----+-----+-----+-----+-----+-----+ 660
 GCCCTACTCGACTGGTTCTGGTCCAGTCGGACTGGACGGACCAGTTCCGAAGATAGGG
 R D E L T K N Q V S L T C L V K G F Y P -
 AGCGACATGCCGTGGAGTGGAGAGCAATGGCAGCCGGAGAACAACTACAAGACCACG
 661 -----+-----+-----+-----+-----+-----+ 720
 TCGCTGTAGCGGCACCTCACCTCTCGTTACCGTCGGCTCTGTTGATGTTCTGGTGC
 S D I A V E W E S N G Q P E N N Y K T T -
 CCTCCCGTGTGGACTCCGACGGCTCCTCTCCTCTACAGCAAGCTCACCGTGGACAAG
 721 -----+-----+-----+-----+-----+-----+ 780
 GGAGGGCACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTGAGTGGCACCTGTC
 P P V L D S D G S F F L Y S K L T V D K -
 AGCAGGTGGCAGCAGGGAACGTCTCTCATGCTCCGTATGCATGAGGCTCTGCACAAAC
 781 -----+-----+-----+-----+-----+-----+ 840
 TCGTCCACCGTCGTCCCTTGAGAACAGAGTACGAGGCACTACGTACTCCGAGACGTGTTG
 S R W Q Q G N V F S C S V M H E A L H N -
 CACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTAAATAA
 841 -----+-----+-----+-----+-----+ 882
 GTGATGTGCGTCTCTCGGAGAGGGACAGAGGCCATTATT
 H Y T Q K S L S L S P G K * -

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| atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gac gtg agc Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser 35 40 45 | 144 |
| cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 50 55 60 | 192 |
| gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 65 70 75 80 | 240 |
| tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 85 90 95 | 288 |
| ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 100 105 110 | 336 |
| atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln 115 120 125 | 384 |
| gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val 130 135 140 | 432 |
| agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val | 480 |

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| 145 | 150 | 155 | 160 | |
|---|-----|-----|-----|-----|
| gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acc acg cct | | | | 528 |
| Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro | | | | |
| 165 | 170 | 175 | | |
| ccc gtg ctg gac tcc gac ggc tcc ttc ctc tac agc aag ctc acc | | | | 576 |
| Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr | | | | |
| 180 | 185 | 190 | | |
| gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg | | | | 624 |
| Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val | | | | |
| 195 | 200 | 205 | | |
| atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg | | | | 672 |
| Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu | | | | |
| 210 | 215 | 220 | | |
| tct ccg ggt aaa | | | | 684 |
| Ser Pro Gly Lys | | | | |
| 225 | | | | |
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| <211> 228 | | | | |
| <212> PRT | | | | |
| <213> Homo sapiens | | | | |
| <400> 2 | | | | |
| Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu | | | | |
| 1 | 5 | 10 | 15 | |
| Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu | | | | |
| 20 | 25 | 30 | | |
| Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser | | | | |
| 35 | 40 | 45 | | |
| His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu | | | | |
| 50 | 55 | 60 | | |
| Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr | | | | |
| 65 | 70 | 75 | 80 | |
| Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn | | | | |
| 85 | 90 | 95 | | |
| Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro | | | | |
| 100 | 105 | 110 | | |
| Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln | | | | |
| 115 | 120 | 125 | | |
| Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val | | | | |
| 130 | 135 | 140 | | |
| Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val | | | | |
| 145 | 150 | 155 | 160 | |

A-743 PCT.ST25.txt

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 195 200 205

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 1 5 10 15

49

gga ggc ggt ggg g
 Gly Gly Gly Gly
 20

62

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 <212> PRT
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 1 5 10 15

Gly Gly Gly Gly
 20

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 <213> Artificial Sequence

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 Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly
 1 5 10 15

gga ggc ggt ggg g 62
 Gly Gly Gly Gly
 20

<210> 6
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
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 1 5 10 15

Gly Gly Gly Gly
 20

<210> 7
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 <213> Artificial Sequence

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<220>
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 <222> (2)..(61)
 <223>

<400> 7
 t atg gtt ccg ttc tgt gac ctg ctg act aaa cac tgt ttc gaa gct ggt 49
 Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly
 1 5 10 15

gga ggc ggt ggg g 62
 Gly Gly Gly Gly
 20

<210> 8
 <211> 20
 <212> PRT
 <213> Artificial Sequence

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<400> 8

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Pro | Phe | Cys | Asp | Leu | Leu | Thr | Lys | His | Cys | Phe | Glu | Ala | Gly |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |

| | | | |
|-----|-----|-----|-----|
| Gly | Gly | Gly | Gly |
| 20 | | | |

<210> 9

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<212> DNA

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| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| t | atg | ggt | tct | cgt | tgt | aaa | tac | aaa | tgg | gac | gtt | ctg | act | aaa | cag | tgt |
| Met | Gly | Ser | Arg | Cys | Lys | Tyr | Lys | | Trp | Asp | Val | Leu | Thr | Lys | Gln | Cys |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | |

49

| | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|---|
| ttc | cac | cac | ggg | gga | ggc | ggg | g |
| Phe | His | His | Gly | Gly | Gly | Gly | |
| 20 | | | | | | | |

74

<210> 10

<211> 24

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<223> NdeI to SalI fragments

<400> 10

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Ser | Arg | Cys | Lys | Tyr | Lys | Trp | Asp | Val | Leu | Thr | Lys | Gln | Cys |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |

| | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|--|
| Phe | His | His | Gly | Gly | Gly | Gly | |
| 20 | | | | | | | |

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1 5 10 15

gac ccg ctg ggt gga ggc ggt ggg g 74
Asp Pro Leu Gly Gly Gly Gly
20

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1 5 10 15

Asp Pro Leu Gly Gly Gly Gly
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1 5 10 15

act tct tct ggt gga ggc ggt ggg g 74
Thr Ser Ser Gly Gly Gly Gly
20

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1 5 10 15

Thr Ser Ser Gly Gly Gly Gly
20

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 Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys 49
 1 5 10 15

tct aac ctg ggt gga ggc ggt ggg g
 Ser Asn Leu Gly Gly Gly Gly 74
 20

<210> 16
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 1 5 10 15

Ser Asn Leu Gly Gly Gly Gly
 20

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 Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys 49
 1 5 10 15

cag ttc aac ggg gtg gag gcg gtg ggg
 Gln Phe Asn Gly Val Glu Ala Val 76
 20

A-743 PCT.ST25.txt

<210> 18
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 1 5 10 15

Gln Phe Asn Gly Val Glu Ala Val
 20

<210> 19
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 Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
 1 5 10 15

cac ggt ctg ggt gga ggc ggt ggg g 74
 His Gly Leu Gly Gly Gly Gly
 20

<210> 20
 <211> 24
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 1 5 10 15

His Gly Leu Gly Gly Gly Gly
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ccg tct ccg ggt gga ggc ggt ggg g 74
 Pro Ser Pro Gly Gly Gly Gly
 20

<210> 22
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<400> 22

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 1 5 10 15

Pro Ser Pro Gly Gly Gly Gly
 20

<210> 23
 <211> 74
 <212> DNA
 <213> Artificial Sequence

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 <223> NdeI to SalI fragments

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 <222> (2)..(73)
 <223>

<400> 23
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 Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Leu Lys Lys Asn Val Cys
 1 5 10 15

gaa ttc ttc ggt gga ggc ggt ggg g 74
 Glu Phe Phe Gly Gly Gly Gly
 20

<210> 24
 <211> 24
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> NdeI to SalI fragments

<400> 24

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Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Leu Lys Lys Asn Val Cys
 1 5 10 15

Glu Phe Phe Gly Gly Gly Gly
 20

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 <211> 74
 <212> DNA
 <213> Artificial Sequence

<220>
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<220>
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 1 5 10 15

cac ggt ctg ggt gga ggc ggt ggg g 74
 His Gly Leu Gly Gly Gly Gly
 20

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 <211> 24
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> NdeI to SalI fragments

<400> 26

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 1 5 10 15

His Gly Leu Gly Gly Gly Gly
 20

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 <212> DNA
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 <223> pAMG21-RANK-Fc vector

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 ggaaacggga aaaagcaagt tttccccgtt cccggcggtt caataactga aaaccataact
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 gatcttcgtc acaattctca agtcgctgtat ttcaaaaaac tgcgttatcc tctgcgaaac
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 240
 300

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| | |
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| tggccgttgt tgcaagaaaa cgtcttacac acaaagagat aaaagttttt gtcaaaaatc | 420 |
| ctctgaagga tctcatggtt gagtactgctc agagagaggg gataacacag gctcagttcg | 480 |
| ttgagaaaaat catcaaagat gaactgctaa gactggatat actaaagtaa agactttact | 540 |
| ttgtggcgta gcatgctaga ttactgatcg tttaaggaat tttgtggctg gccacgcccgt | 600 |
| aaggtggcaa ggaactggtt ctgatgtgga tttacaggag ccagaaaagc aaaaaccccg | 660 |
| ataatcttct tcaacttttg cgagtacgaa aagattaccg gggcccactt aaaccgtata | 720 |
| gccaacaatt cagctatgctc gggagtatacg ttatatgccc ggaaaagttc aagacttctt | 780 |
| tctgtgctcg ctcccttctgc gcattgtaaag tgcaggatgg tgtgactgtat cttcaccaaa | 840 |
| cgtattaccg ccaggtaaag aacccgaatc cggtgtttac accccgtgaa ggtgcaggaa | 900 |
| cgctgaagtt ctgcgaaaaaa ctgatggaaa aggccgtggg cttcaattcc cgttttgatt | 960 |
| tcgcccattca tgtggcgcac gcccgttcgc gtatctgctc tcgcccgtatg ccaccagtgc | 1020 |
| tgcgtcgctcg ggctattgtat ggcgtcttgc agggctgtg tttccactat gacccgctgg | 1080 |
| ccaaaccgcgt ccagtgcctcc atcaccacgc tggccattga gtgcggactg ggcacggagt | 1140 |
| ctgctgccgg aaaactctcc atcaccctgtc ccaccgtgc cctgacgttc ctgtcagac | 1200 |
| tgggactgtat tacctaccag acggaatatg acccgcttac cgggtgctac attccgaccg | 1260 |
| atatcacgtt cacatctgca ctgtttgtc ccctcgatgt atcagaggag gcagtggccg | 1320 |
| ccgcgcgcgc cagccgtgtg gtatggaaa acaaacaacg caaaaagcag gggctggata | 1380 |
| ccctggccat ggatgaactg atagcgaaag cctggcgaaa ttgcgtgag cgtttcgc | 1440 |
| gttatcagac agagcttaag tcccgtggaa taaagcgtgc ccgtgcgcgt cgtatgcgg | 1500 |
| acagggaaacg tcaggatatt gtcaccctgg taaaacggca gctgacgcgc gaaatgcgg | 1560 |
| aaggccgtt cactgccaat cgtgaggcgg taaaacgcga agttgagcgt cgtgtgaagg | 1620 |
| agcgcacatgtat tctgtcacgt aaccgttaatt acagccggct ggccacagct tccccctgaa | 1680 |
| agtgacctcc tctgaataat ccggcctgcg ccggaggctt ccgcacgtct gaagccgcac | 1740 |
| agcgcacaaa aaatcagcac cacataaaaaa aaacaacctc atcatccagc ttctggtgca | 1800 |
| tccggccccc cctgtttcg atacaaaaca cgcctcacag acggggatt ttgcattatcc | 1860 |
| acattaaact gcaaggact tccccataag gttacaaccg ttcatgtcat aaagcgccat | 1920 |
| ccgcccagcgt tacaggggtgc aatgtatctt taaaacacct gtttatatct cctttaaact | 1980 |
| acttaattac attcattaa aaagaaaaacc tattcactgc ctgtccttgg acagacagat | 2040 |
| atgcacccccc caccgcaagc ggcggccccc taccggagcc gctttagttt caacactcag | 2100 |
| acacaaccac cagaaaaacc ccggtccagc gcagaactga aaccacaaaag cccctccctc | 2160 |
| ataactgaaa agcggccccc ccccggtccg aaggccggaa acagagtcgc ttttaattat | 2220 |
| gaatgttgta actacttcat catcgctgtc agtcttctcg ctggaaatgc tcagttacacg | 2280 |
| ctcgtaagcg gcccgtacgg cccgctaaccg cgagataccg ccccgacttc gggtaaacc | 2340 |

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| | |
|--|------|
| tcgtcgggac cactccgacc gcgcacagaa gctctctcat ggctgaaagc gggtatggtc | 2400 |
| tggcagggct gggatgggt aaggtgaaat ctatcaatca gtaccggctt acgcccggct | 2460 |
| tcggcggtt tactcctgtt tcatatatga aacaacaggt caccgccttc catgccgctg | 2520 |
| atgcggcata tcctggtaac gatatctgaa ttgttataca tgtgtatata cgtggtaatg | 2580 |
| acaaaaatag gacaagttaa aaatttacag gcgatgcaat gattcaaaca cgtaatcaat | 2640 |
| atcgggggtg ggcgaagaac tccagcatga gatccccgctg ctggaggatc atccagccgg | 2700 |
| cgtcccgaa aacgattccg aagcccaacc tttcatagaa ggcggcggtg gaatcgaaat | 2760 |
| ctcgtatgg caggttggc gtcgcttggt cggtcatttc gaaccccaga gtcccgtca | 2820 |
| gaagaactcg tcaagaaggc gatagaaggc gatgcgcgtc gaatcgggag cggcgatacc | 2880 |
| gtaaagcacg aggaagcggt cagcccatc gcccacaagc tcttcagcaa tatcacgggt | 2940 |
| agccaaacgct atgtcctgat agcggtccgc cacacccagc cggccacagt cgatgaatcc | 3000 |
| agaaaagcgg ccattttcca ccatgatatt cggcaagcag gcatcgccat gagtcacgac | 3060 |
| gagatcctcg ccgtcggca tgcgcgcctt gagcctggcg aacagttcgg ctggcgcgag | 3120 |
| cccctgatgc tttcgtcca gatcatcctg atcgacaaga ccggcttcca tccgagtacg | 3180 |
| tgctcgctcg atgcgtatgtt tgccttggc gtcgaatggg caggtagccg gatcaagcgt | 3240 |
| atgcagccgc cgcattgcat cagccatgat ggatactttc tcggcaggag caaggtgaga | 3300 |
| tgacaggaga tcctgccccg gcacttcgcc caatacgagc cagtccttc ccgcctcagt | 3360 |
| gacaacgtcg agcacagctg cgcaaggaac gcccgtcg gccagccacg atagccgcgc | 3420 |
| tgcctcggtcc tgcaattcat tcaggacacc ggacaggtcg gtcttgacaa aaagaaccgg | 3480 |
| gcccctgtc gctgacagcc ggaacacggc ggcacatcgag cagccgattt tctgttgtgc | 3540 |
| ccagtcatacg ccgaatagcc tctccacca agcggccggaa gAACCTGCGT gcaatccatc | 3600 |
| ttgttcaatc atgcgaaacg atcctcatcc tgtcttttga tctgatcttgc atcccctgc | 3660 |
| ccatcagatc cttggcggca agaaagccat ccagttact ttgcagggtt tcccaacctt | 3720 |
| accagagggc gccccagctg gcaattccgg ttcgcttgcgt gtccataaaaa ccgcccagtc | 3780 |
| tagctatcgc catgtaagcc cactgcaagc tacctgcttt ctcttgcgc ttgcgttttc | 3840 |
| ccttgcgtccat atagcccaagt agctgacatt catccgggtt cagcaccgtt tctgcggact | 3900 |
| ggctttctac gtgttccgtt tcccttagca gcccctgcgc cctgagtgcgt tgccggcagcg | 3960 |
| tgaagctaca tataatgtat ccgggcaaat cgctgaatat tcctttgtc tccgaccatc | 4020 |
| aggcacctga gtcgctgtct tttcgtgac attcagttcg ctgcgcac ggctctggca | 4080 |
| gtgaatgggg gtaaatggca ctacaggcgc ctttatggaa ttcatgcaag gaaactaccc | 4140 |
| ataatacaag aaaagccgt cacggccttc tcagggcggtt ttatggcggg tctgctatgt | 4200 |
| ggtgctatct gacttttgc tgttcagcag ttccctgcct ctgatccatc agtctgacca | 4260 |
| cttcggattt tccctgtaca ggtcattcag actggctaat gcacccagta aggcagcgg | 4320 |
| atcatcaaca ggcttacccg tcttactgtc gaagacgtgc gtaacgtatg catggtctcc | 4380 |

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| gggccttcg ttttatctgt tggttgcgg tgaacgctct cctgagtagg acaaatccgc | 4500 |
| cgggagcgg a tttgaacgtt gcgaagcaac ggcccgagg gtggcggca ggacgcccgc | 4560 |
| cataaaactgc caggcatcaa attaaggcaga aggccatcct gacggatggc cttttgcgt | 4620 |
| ttctacaaac tctttgttt attttctaa atacattcaa atatggacgt cgtacttaac | 4680 |
| ttttaaagta tgggcaatca attgctcctg ttaaaaattgc ttttagaaata ctttggcagc | 4740 |
| ggtttgttgtt attgagtttc atttgcgcatttggtaatg gaaagtgacc gtgcgcattac | 4800 |
| tacagcctaa tattttgaa atatcccaag agcttttcc ttgcgcatttgc cacgctaaac | 4860 |
| attcttttc tctttgtttt aaatcggtt ttgatttattt atttgcattttt ttttattttc | 4920 |
| gataattatc aactagagaa ggaacaatta atggatgtt catacacgca tgtaaaaata | 4980 |
| aactatctat atagttgtct ttctctgaat gtgcggaaact aagcattccg aagccattat | 5040 |
| tagcagtatg aataggaaa ctaaaccagg tggataagacc tggatgttcc gcttctttaa | 5100 |
| ttacattttgg agatttttta ttacagcat tggtttcaaa tatattccaa ttaatcggtt | 5160 |
| aatgatttggaa gtttagaataa tctactatag gatcatattt tattaaatta ggcgcattcat | 5220 |
| aatattgcct ccattttta gggtaattat ccagaattga aatatcagat ttaaccatag | 5280 |
| aatgaggata aatgatcgcg agttaataat attcacaatg taccattttt gtcatatcag | 5340 |
| ataagcatgg attaataatca ttattgcttc tacaggcttt aatttttattt attattctgt | 5400 |
| aagtgtcgcc ggcattttatg tcttcataccatccatctttt atccttacccatttttgc | 5460 |
| gcaagttttcg cgtttatattt atcattaaaaa cggtaataga ttgacatttgc attctaataa | 5520 |
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| taggatcgta caggtttacg caagaaaatg gtttggataat gtcgatataat cgatttgatt | 5640 |
| ctagattttgt tttaactaat taaaggagga ataacatatg atcgctccac catgcaccag | 5700 |
| tgagaagcat tatgagcatc tgggacggtg ctgttacaaa tggtaaccag gaaagtacat | 5760 |
| gtcttctaaa tgcactacta cctctgacag tggatgtctg ccctgtggcc cggatgaata | 5820 |
| cttggatagc tggaaatgaag aagataaaatg cttgcgcatttgc aatggatgttgc atacaggcaaa | 5880 |
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| tgggttaccac tggagccagg actgcgagtg ctgcccggcgc aacaccggat ggcgcgggg | 6000 |
| cctggggcc cagcacccgt tgcagctaa caaggacaca gtgtgcaaac cttgccttgc | 6060 |
| aggctacttc tctgtatgcct tttcctccac ggacaaatgc agaccctggaa ccaactgtac | 6120 |
| cttccttggaa aagagagtag aacatcatgg gacagagaaa tccgatgtgg tttgcagtgc | 6180 |
| ttctctgcctt gctagaaaac caccaaatga accccatgtt tacgtgcaca aaactcacac | 6240 |
| atgtccaccc tgcacacttc cggaaactccctt ggggggacccg tcaatgcattcc tcttcccccc | 6300 |
| aaaaccccaag gacaccctca tggatctcccg gaccctgag gtcacatgcg tgggtggaa | 6360 |
| cgtgagccac gaagaccctg aggtcaagtt caactggatc gtggacggcg tggaggtgca | 6420 |

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| caaagccctc ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga | 6600 |
| accacaggtg tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct | 6660 |
| gacctgcctg gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg | 6720 |
| gcagccggag aacaactaca agaccacgcc tccctgtctg gactccgacg gctccttctt | 6780 |
| cctctacagc aagctcaccg tggacaagag caggtggcag cagggaaacg tcttctcatg | 6840 |
| ctccgtgatg catgaggctc tgcacaacca ctacacgcag aagagccctc ccctgtctcc | 6900 |
| gggtaaataa tggatccgcg gaaagaagaa gaagaagaag aaagccgaa aggaagctga | 6960 |
| gttggctgct gccaccgctg agcaataact agcataaccc cttggggcct ctaaacgggt | 7020 |
| cttgagggggt ttttgctga aaggaggaac cgctttcac gctttcacg cggataaata | 7080 |
| agtaacgatc cggtccagta atgacctcag aactccatct ggatttggc agaacgctcg | 7140 |
| gttgccgccc ggcgtttttt attggtgaga atcgcagcaa cttgtcgcgc caatcgagcc | 7200 |
| atgtcgtcgt caacgacccc ccattcaaga acagcaagca gcattgagaa ctttggaaatc | 7260 |
| cagtcctct tccacctgct gaccg | 7285 |

<210> 28
<211> 7285
<212> PRT
<213> Artificial Sequence

<220>
<223> pAMG21-RANK-Fc vector

<220>
<221> misc_feature
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Xaa (Pos5,6,7,9,13) are each independently amino acid residues.

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Cys Cys Thr Thr Cys Gly Cys Gly Thr Thr Gly Cys Thr Cys Ala Gly
35 40 45

Thr Thr Gly Thr Cys Cys Ala Ala Cys Cys Cys Gly Gly Ala Ala
50 55 60

Ala Cys Gly Gly Ala Ala Ala Ala Gly Cys Ala Ala Gly Thr
65 70 75 80

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Thr Thr Thr Cys Cys Cys Gly Cys Thr Cys Cys Cys Gly Gly Cys
85 90 95

Gly Thr Thr Thr Cys Ala Ala Thr Ala Ala Cys Thr Gly Ala Ala Ala
100 105 110

Ala Cys Cys Ala Thr Ala Cys Thr Ala Thr Thr Cys Ala Cys Ala
115 120 125

Gly Thr Thr Thr Ala Ala Ala Thr Cys Ala Cys Ala Thr Thr Ala Ala
130 135 140

Ala Cys Gly Ala Cys Ala Gly Thr Ala Ala Thr Cys Cys Cys Cys Gly
145 150 155 160

Thr Thr Gly Ala Thr Thr Gly Thr Gly Cys Gly Cys Cys Ala Ala
165 170 175

Cys Ala Cys Ala Gly Ala Thr Cys Thr Thr Cys Gly Thr Cys Ala Cys
180 185 190

Ala Ala Thr Thr Cys Thr Cys Ala Ala Gly Thr Cys Gly Cys Thr Gly
195 200 205

Ala Thr Thr Thr Cys Ala Ala Ala Ala Ala Cys Thr Gly Thr Ala
210 215 220

Gly Thr Ala Thr Cys Cys Thr Cys Thr Gly Cys Gly Ala Ala Ala Cys
225 230 235 240

Gly Ala Thr Cys Cys Cys Thr Gly Thr Thr Gly Ala Gly Thr Ala
245 250 255

Thr Thr Gly Ala Gly Gly Ala Gly Gly Cys Gly Ala Gly Ala Thr Gly
260 265 270

Thr Cys Gly Cys Ala Gly Ala Cys Ala Gly Ala Ala Ala Ala Thr Gly
275 280 285

Cys Ala Gly Thr Gly Ala Cys Thr Thr Cys Cys Thr Cys Ala Thr Thr
290 295 300

Gly Ala Gly Thr Cys Ala Ala Ala Ala Gly Cys Gly Gly Thr Thr Thr
305 310 315 320

Gly Thr Gly Cys Gly Cys Ala Gly Ala Gly Gly Thr Ala Ala Gly Cys
325 330 335

Cys Thr Ala Thr Gly Ala Cys Thr Gly Ala Cys Thr Cys Thr Gly Ala
340 345 350

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355 360 365

Gly Thr Thr Gly Cys Ala Ala Gly Ala Ala Ala Cys Gly Thr Cys
370 375 380

Thr Thr Ala Cys Ala Cys Ala Cys Ala Ala Gly Ala Gly Ala Thr
385 390 395 400

Ala Ala Ala Ala Gly Thr Thr Thr Gly Thr Cys Ala Ala Ala
405 410 415

Ala Ala Thr Cys Cys Thr Cys Thr Gly Ala Ala Gly Gly Ala Thr Cys
420 425 430

Thr Cys Ala Thr Gly Gly Thr Thr Gly Ala Gly Thr Ala Cys Thr Gly
435 440 445

Cys Gly Ala Gly Ala Gly Ala Gly Gly Gly Ala Thr Ala
450 455 460

Ala Cys Ala Cys Ala Gly Gly Cys Thr Cys Ala Gly Thr Thr Cys Gly
465 470 475 480

Thr Thr Gly Ala Gly Ala Ala Ala Ala Thr Cys Ala Thr Cys Ala Ala
485 490 495

Ala Gly Ala Thr Gly Ala Ala Cys Thr Gly Cys Ala Ala Ala Gly Ala
500 505 510

Cys Thr Gly Gly Ala Thr Ala Cys Thr Ala Ala Ala Gly Thr
515 520 525

Ala Ala Ala Gly Ala Cys Thr Thr Ala Cys Thr Thr Thr Gly Thr
530 535 540

Gly Gly Cys Gly Thr Ala Gly Cys Ala Thr Gly Cys Thr Ala Gly Ala
545 550 555 560

Thr Thr Ala Cys Thr Gly Ala Thr Cys Gly Thr Thr Thr Ala Ala Gly
565 570 575

Gly Ala Ala Thr Thr Thr Gly Thr Gly Gly Cys Thr Gly Gly Cys
580 585 590

Cys Ala Cys Gly Cys Cys Gly Thr Ala Ala Gly Gly Thr Gly Gly Cys
595 600 605

Ala Ala Gly Gly Ala Ala Cys Thr Gly Gly Thr Thr Cys Thr Gly Ala
610 615 620

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Thr Gly Thr Gly Gly Ala Thr Thr Thr Ala Cys Ala Gly Gly Ala Gly
625 630 635 640

Cys Cys Ala Gly Ala Ala Ala Gly Cys Ala Ala Ala Ala Ala Cys
645 650 655

Cys Cys Cys Gly Ala Thr Ala Ala Thr Cys Thr Thr Cys Thr Cys
660 665 670

Ala Ala Cys Thr Thr Thr Gly Cys Gly Ala Gly Thr Ala Cys Gly
675 680 685

Ala Ala Ala Ala Gly Ala Thr Thr Ala Cys Cys Gly Gly Gly Cys
690 695 700

Cys Cys Ala Cys Thr Thr Ala Ala Ala Cys Cys Gly Thr Ala Thr Ala
705 710 715 720

Gly Cys Cys Ala Ala Cys Ala Ala Thr Thr Cys Ala Gly Cys Thr Ala
725 730 735

Thr Gly Cys Gly Gly Gly Ala Gly Thr Ala Thr Ala Gly Thr Thr
740 745 750

Ala Thr Ala Thr Gly Cys Cys Gly Gly Ala Ala Ala Ala Gly Thr
755 760 765

Thr Cys Ala Ala Gly Ala Cys Thr Thr Cys Thr Thr Cys Thr Gly
770 775 780

Thr Gly Cys Thr Cys Gly Cys Thr Cys Cys Thr Thr Cys Thr Gly Cys
785 790 795 800

Gly Cys Ala Thr Thr Gly Thr Ala Ala Gly Thr Gly Cys Ala Gly Gly
805 810 815

Ala Thr Gly Gly Thr Gly Ala Cys Thr Gly Ala Thr Cys Thr
820 825 830

Thr Cys Ala Cys Cys Ala Ala Ala Cys Gly Thr Ala Thr Thr Ala Cys
835 840 845

Cys Gly Cys Cys Ala Gly Gly Thr Ala Ala Ala Gly Ala Ala Cys Cys
850 855 860

Cys Gly Ala Ala Thr Cys Cys Gly Gly Thr Gly Thr Thr Thr Ala Cys
865 870 875 880

Ala Cys Cys Cys Cys Gly Thr Gly Ala Ala Gly Gly Thr Gly Cys Ala
885 890 895

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Gly Gly Ala Ala Cys Gly Cys Thr Gly Ala Ala Gly Thr Thr Cys Thr
900 905 910

Gly Cys Gly Ala Ala Ala Ala Cys Thr Gly Ala Thr Gly Gly Ala
915 920 925

Ala Ala Ala Gly Gly Cys Gly Thr Gly Gly Cys Thr Thr Cys
930 935 940

Ala Cys Thr Thr Cys Cys Cys Gly Thr Thr Thr Thr Gly Ala Thr Thr
945 950 955 960

Thr Cys Gly Cys Cys Ala Thr Thr Cys Ala Thr Gly Thr Gly Gly Cys
965 970 975

Gly Cys Ala Cys Gly Cys Cys Cys Gly Thr Thr Cys Gly Cys Gly Thr
980 985 990

Gly Ala Thr Cys Thr Gly Cys Gly Thr Cys Gly Cys Cys Gly Thr Ala
995 1000 1005

Thr Gly Cys Cys Ala Cys Cys Ala Gly Thr Gly Cys Thr Gly Cys
1010 1015 1020

Gly Thr Cys Gly Thr Cys Gly Gly Gly Cys Thr Ala Thr Thr Gly
1025 1030 1035

Ala Thr Gly Cys Gly Cys Thr Cys Thr Thr Gly Cys Ala Gly Gly
1040 1045 1050

Gly Gly Cys Thr Gly Thr Gly Thr Thr Thr Cys Cys Ala Cys Thr
1055 1060 1065

Ala Thr Gly Ala Cys Cys Cys Gly Cys Thr Gly Gly Cys Cys Ala
1070 1075 1080

Ala Cys Cys Gly Cys Gly Thr Cys Cys Ala Gly Thr Gly Cys Thr
1085 1090 1095

Cys Cys Ala Thr Cys Ala Cys Cys Ala Cys Gly Cys Thr Gly Gly
1100 1105 1110

Cys Cys Ala Thr Thr Gly Ala Gly Thr Gly Cys Gly Gly Ala Cys
1115 1120 1125

Thr Gly Gly Cys Gly Ala Cys Gly Gly Ala Gly Thr Cys Thr Gly
1130 1135 1140

Cys Thr Gly Cys Cys Gly Gly Ala Ala Ala Ala Cys Thr Cys Thr
1145 1150 1155

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Cys Cys Ala Thr Cys Ala Cys Cys Cys Gly Thr Gly Cys Cys Ala
1160 1165 1170

Cys Cys Cys Gly Thr Gly Cys Cys Cys Thr Gly Ala Cys Gly Thr
1175 1180 1185

Thr Cys Cys Thr Gly Thr Cys Ala Gly Ala Gly Cys Thr Gly Gly
1190 1195 1200

Gly Ala Cys Thr Gly Ala Thr Thr Ala Cys Cys Thr Ala Cys Cys
1205 1210 1215

Ala Gly Ala Cys Gly Gly Ala Ala Thr Ala Thr Gly Ala Cys Cys
1220 1225 1230

Cys Gly Cys Thr Thr Ala Thr Cys Gly Gly Gly Thr Gly Cys Thr
1235 1240 1245

Ala Cys Ala Thr Thr Cys Cys Gly Ala Cys Cys Gly Ala Thr Ala
1250 1255 1260

Thr Cys Ala Cys Gly Thr Thr Cys Ala Cys Ala Thr Cys Thr Gly
1265 1270 1275

Cys Ala Cys Thr Gly Thr Thr Gly Cys Thr Gly Cys Cys Cys
1280 1285 1290

Thr Cys Gly Ala Thr Gly Thr Ala Thr Cys Ala Gly Ala Gly Gly
1295 1300 1305

Ala Gly Gly Cys Ala Gly Thr Gly Gly Cys Cys Gly Cys Cys Gly
1310 1315 1320

Cys Gly Cys Gly Cys Cys Gly Cys Ala Gly Cys Cys Gly Thr Gly
1325 1330 1335

Thr Gly Gly Thr Ala Thr Gly Gly Gly Ala Ala Ala Ala Cys Ala
1340 1345 1350

Ala Ala Cys Ala Ala Cys Gly Cys Ala Ala Ala Ala Ala Gly Cys
1355 1360 1365

Ala Gly Gly Gly Gly Cys Thr Gly Gly Ala Thr Ala Cys Cys Cys
1370 1375 1380

Thr Gly Gly Gly Cys Ala Thr Gly Gly Ala Thr Gly Ala Ala Cys
1385 1390 1395

Thr Gly Ala Thr Ala Gly Cys Gly Ala Ala Ala Gly Cys Cys Thr
1400 1405 1410

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Gly Gly Cys Gly Thr Thr Thr Gly Thr Thr Cys Gly Thr Gly
1415 1420 1425

Ala Gly Cys Gly Thr Thr Thr Cys Gly Cys Ala Gly Thr Thr
1430 1435 1440

Ala Thr Cys Ala Gly Ala Cys Ala Gly Ala Gly Cys Thr Thr Ala
1445 1450 1455

Ala Gly Thr Cys Cys Cys Gly Thr Gly Gly Ala Ala Thr Ala Ala
1460 1465 1470

Ala Gly Cys Gly Thr Gly Cys Cys Cys Gly Thr Gly Cys Gly Cys
1475 1480 1485

Gly Thr Cys Gly Thr Gly Ala Thr Gly Cys Gly Gly Ala Cys Ala
1490 1495 1500

Gly Gly Gly Ala Ala Cys Gly Thr Cys Ala Gly Gly Ala Thr Ala
1505 1510 1515

Thr Thr Gly Thr Cys Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala
1520 1525 1530

Ala Ala Cys Gly Gly Cys Ala Gly Cys Thr Gly Ala Cys Gly Cys
1535 1540 1545

Gly Cys Gly Ala Ala Ala Thr Cys Gly Cys Gly Gly Ala Ala Gly
1550 1555 1560

Gly Gly Cys Gly Cys Thr Thr Cys Ala Cys Thr Gly Cys Cys Ala
1565 1570 1575

Ala Thr Cys Gly Thr Gly Ala Gly Gly Cys Gly Gly Thr Ala Ala
1580 1585 1590

Ala Ala Cys Gly Cys Gly Ala Ala Gly Thr Thr Gly Ala Gly Cys
1595 1600 1605

Gly Thr Cys Gly Thr Gly Thr Gly Ala Ala Gly Gly Ala Gly Cys
1610 1615 1620

Gly Cys Ala Thr Gly Ala Thr Thr Cys Thr Gly Thr Cys Ala Cys
1625 1630 1635

Gly Thr Ala Ala Cys Cys Gly Thr Ala Ala Thr Thr Ala Cys Ala
1640 1645 1650

Gly Cys Cys Gly Gly Cys Thr Gly Gly Cys Cys Ala Cys Ala Gly
1655 1660 1665

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Cys Thr Thr Cys Cys Cys Cys Cys Thr Gly Ala Ala Ala Gly Thr
1670 1675 1680

Gly Ala Cys Cys Thr Cys Cys Thr Cys Thr Gly Ala Ala Thr Ala
1685 1690 1695

Ala Thr Cys Cys Gly Gly Cys Cys Thr Gly Cys Gly Cys Cys Gly
1700 1705 1710

Gly Ala Gly Gly Cys Thr Thr Cys Cys Gly Cys Ala Cys Gly Thr
1715 1720 1725

Cys Thr Gly Ala Ala Gly Cys Cys Cys Gly Ala Cys Ala Gly Cys
1730 1735 1740

Gly Cys Ala Cys Ala Ala Ala Ala Ala Ala Ala Thr Cys Ala Gly Cys
1745 1750 1755

Ala Cys Cys Ala Cys Ala Thr Ala Cys Ala Ala Ala Ala Ala Ala
1760 1765 1770

Cys Ala Ala Cys Cys Thr Cys Ala Thr Cys Ala Thr Cys Cys Ala
1775 1780 1785

Gly Cys Thr Thr Cys Thr Gly Gly Thr Gly Cys Ala Thr Cys Cys
1790 1795 1800

Gly Gly Cys Cys Cys Cys Cys Cys Cys Thr Gly Thr Thr Thr
1805 1810 1815

Cys Gly Ala Thr Ala Cys Ala Ala Ala Ala Cys Ala Cys Gly Cys
1820 1825 1830

Cys Thr Cys Ala Cys Ala Gly Ala Cys Gly Gly Gly Ala Ala
1835 1840 1845

Thr Thr Thr Thr Gly Cys Thr Thr Ala Thr Cys Cys Ala Cys Ala
1850 1855 1860

Thr Thr Ala Ala Ala Cys Thr Gly Cys Ala Ala Gly Gly Gly Ala
1865 1870 1875

Cys Thr Thr Cys Cys Cys Cys Ala Thr Ala Ala Gly Gly Thr Thr
1880 1885 1890

Ala Cys Ala Ala Cys Cys Gly Thr Thr Cys Ala Thr Gly Thr Cys
1895 1900 1905

Ala Thr Ala Ala Ala Gly Cys Gly Cys Cys Ala Thr Cys Cys Gly
1910 1915 1920

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Cys Cys Ala Gly Cys Gly Thr Thr Ala Cys Ala Gly Gly Gly Thr
1925 1930 1935

Gly Cys Ala Ala Thr Gly Thr Ala Thr Cys Thr Thr Thr Ala
1940 1945 1950

Ala Ala Cys Ala Cys Cys Thr Gly Thr Thr Ala Thr Ala Thr
1955 1960 1965

Cys Thr Cys Cys Thr Thr Ala Ala Ala Cys Thr Ala Cys Thr
1970 1975 1980

Thr Ala Ala Thr Thr Ala Cys Ala Thr Thr Cys Ala Thr Thr Thr
1985 1990 1995

Ala Ala Ala Ala Ala Gly Ala Ala Ala Ala Cys Cys Thr Ala Thr
2000 2005 2010

Thr Cys Ala Cys Thr Gly Cys Cys Thr Gly Thr Cys Cys Thr Thr
2015 2020 2025

Gly Gly Ala Cys Ala Gly Ala Cys Ala Gly Ala Thr Ala Thr Gly
2030 2035 2040

Cys Ala Cys Cys Thr Cys Cys Cys Ala Cys Cys Gly Cys Ala Ala
2045 2050 2055

Gly Cys Gly Gly Cys Gly Gly Cys Cys Cys Cys Cys Thr Ala Cys
2060 2065 2070

Cys Gly Gly Ala Gly Cys Cys Gly Cys Thr Thr Ala Gly Thr
2075 2080 2085

Thr Ala Cys Ala Ala Cys Ala Cys Thr Cys Ala Gly Ala Cys Ala
2090 2095 2100

Cys Ala Ala Cys Cys Ala Cys Cys Ala Gly Ala Ala Ala Ala Ala
2105 2110 2115

Cys Cys Cys Cys Gly Gly Thr Cys Cys Ala Gly Cys Gly Cys Ala
2120 2125 2130

Gly Ala Ala Cys Thr Gly Ala Ala Ala Cys Cys Ala Cys Ala Ala
2135 2140 2145

Ala Gly Cys Cys Cys Cys Thr Cys Cys Cys Thr Cys Ala Thr Ala
2150 2155 2160

Ala Cys Thr Gly Ala Ala Ala Gly Cys Gly Gly Cys Cys Cys
2165 2170 2175

A-743 PCT.ST25.txt

Cys Gly Cys Cys Cys Cys Gly Gly Thr Cys Cys Gly Ala Ala Gly
2180 2185 2190

Gly Gly Cys Cys Gly Gly Ala Ala Cys Ala Gly Ala Gly Thr Cys
2195 2200 2205

Gly Cys Thr Thr Thr Ala Ala Thr Thr Ala Thr Gly Ala Ala
2210 2215 2220

Thr Gly Thr Thr Gly Thr Ala Ala Cys Thr Ala Cys Thr Thr Cys
2225 2230 2235

Ala Thr Cys Ala Thr Cys Gly Cys Thr Gly Thr Cys Ala Gly Thr
2240 2245 2250

Cys Thr Thr Cys Thr Cys Gly Cys Thr Gly Gly Ala Ala Gly Thr
2255 2260 2265

Thr Cys Thr Cys Ala Gly Thr Ala Cys Ala Cys Gly Cys Thr Cys
2270 2275 2280

Gly Thr Ala Ala Gly Cys Gly Gly Cys Cys Cys Thr Gly Ala Cys
2285 2290 2295

Gly Gly Cys Cys Cys Gly Cys Thr Ala Ala Cys Gly Cys Gly Gly
2300 2305 2310

Ala Gly Ala Thr Ala Cys Gly Cys Cys Cys Cys Gly Ala Cys Thr
2315 2320 2325

Thr Cys Gly Gly Gly Thr Ala Ala Ala Cys Cys Cys Thr Cys Gly
2330 2335 2340

Thr Cys Gly Gly Gly Ala Cys Cys Ala Cys Thr Cys Cys Gly Ala
2345 2350 2355

Cys Cys Gly Cys Gly Cys Ala Cys Ala Gly Ala Ala Gly Cys Thr
2360 2365 2370

Cys Thr Cys Thr Cys Ala Thr Gly Gly Cys Thr Gly Ala Ala Ala
2375 2380 2385

Gly Cys Gly Gly Gly Thr Ala Thr Gly Gly Thr Cys Thr Gly Gly
2390 2395 2400

Cys Ala Gly Gly Gly Cys Thr Gly Gly Gly Ala Thr Gly Gly
2405 2410 2415

Gly Thr Ala Ala Gly Gly Thr Gly Ala Ala Ala Thr Cys Thr Ala
2420 2425 2430

A-743 PCT.ST25.txt

Thr Cys Ala Ala Thr Cys Ala Gly Thr Ala Cys Cys Gly Gly Cys
2435 2440 2445

Thr Thr Ala Cys Gly Cys Cys Gly Gly Gly Cys Thr Thr Cys Gly
2450 2455 2460

Gly Cys Gly Gly Thr Thr Thr Ala Cys Thr Cys Cys Thr Gly
2465 2470 2475

Thr Thr Thr Cys Ala Thr Ala Thr Ala Thr Gly Ala Ala Ala Cys
2480 2485 2490

Ala Ala Cys Ala Gly Gly Thr Cys Ala Cys Cys Gly Cys Cys Thr
2495 2500 2505

Thr Cys Cys Ala Thr Gly Cys Cys Gly Cys Thr Gly Ala Thr Gly
2510 2515 2520

Cys Gly Gly Cys Ala Thr Ala Thr Cys Cys Cys Thr Gly Gly Thr Ala
2525 2530 2535

Ala Cys Gly Ala Thr Ala Thr Cys Thr Gly Ala Ala Thr Thr Gly
2540 2545 2550

Thr Thr Ala Thr Ala Cys Ala Thr Gly Thr Gly Thr Ala Thr Ala
2555 2560 2565

Thr Ala Cys Gly Thr Gly Gly Thr Ala Ala Thr Gly Ala Cys Ala
2570 2575 2580

Ala Ala Ala Ala Thr Ala Gly Gly Ala Cys Ala Ala Gly Thr Thr
2585 2590 2595

Ala Ala Ala Ala Ala Thr Thr Thr Ala Cys Ala Gly Gly Cys Gly
2600 2605 2610

Ala Thr Gly Cys Ala Ala Thr Gly Ala Thr Thr Cys Ala Ala Ala
2615 2620 2625

Cys Ala Cys Gly Thr Ala Ala Thr Cys Ala Ala Thr Ala Thr Cys
2630 2635 2640

Gly Gly Gly Gly Thr Gly Gly Gly Cys Gly Ala Ala Gly Ala
2645 2650 2655

Ala Cys Thr Cys Cys Ala Gly Cys Ala Thr Gly Ala Gly Ala Thr
2660 2665 2670

Cys Cys Cys Cys Gly Cys Gly Cys Thr Gly Gly Ala Gly Gly Ala
2675 2680 2685

A-743 PCT.ST25.txt

Thr Cys Ala Thr Cys Cys Ala Gly Cys Cys Gly Gly Cys Gly Thr
2690 2695 2700

Cys Cys Cys Gly Gly Ala Ala Ala Ala Cys Gly Ala Thr Thr Cys
2705 2710 2715

Cys Gly Ala Ala Gly Cys Cys Cys Ala Ala Cys Cys Thr Thr Thr
2720 2725 2730

Cys Ala Thr Ala Gly Ala Ala Gly Gly Cys Gly Gly Cys Gly Gly
2735 2740 2745

Thr Gly Gly Ala Ala Thr Cys Gly Ala Ala Ala Thr Cys Thr Cys
2750 2755 2760

Gly Thr Gly Ala Thr Gly Gly Cys Ala Gly Gly Thr Thr Gly Gly
2765 2770 2775

Gly Cys Gly Thr Cys Gly Cys Thr Thr Gly Gly Thr Cys Gly Gly
2780 2785 2790

Thr Cys Ala Thr Thr Thr Cys Gly Ala Ala Cys Cys Cys Cys Ala
2795 2800 2805

Gly Ala Gly Thr Cys Cys Cys Gly Cys Thr Cys Ala Gly Ala Ala
2810 2815 2820

Gly Ala Ala Cys Thr Cys Gly Thr Cys Ala Ala Gly Ala Ala Gly
2825 2830 2835

Gly Cys Gly Ala Thr Ala Gly Ala Ala Gly Gly Cys Gly Ala Thr
2840 2845 2850

Gly Cys Gly Cys Thr Gly Cys Gly Ala Ala Thr Cys Gly Gly Gly
2855 2860 2865

Ala Gly Cys Gly Gly Cys Gly Ala Thr Ala Cys Cys Gly Thr Ala
2870 2875 2880

Ala Ala Gly Cys Ala Cys Gly Ala Gly Gly Ala Ala Gly Cys Gly
2885 2890 2895

Gly Thr Cys Ala Gly Cys Cys Cys Ala Thr Thr Cys Gly Cys Cys
2900 2905 2910

Gly Cys Cys Ala Ala Gly Cys Thr Cys Thr Thr Cys Ala Gly Cys
2915 2920 2925

Ala Ala Thr Ala Thr Cys Ala Cys Gly Gly Thr Ala Gly Cys
2930 2935 2940

A-743 PCT.ST25.txt

Cys Ala Ala Cys Gly Cys Thr Ala Thr Gly Thr Cys Cys Thr Gly
2945 2950 2955

Ala Thr Ala Gly Cys Gly Gly Thr Cys Cys Gly Cys Cys Ala Cys
2960 2965 2970

Ala Cys Cys Cys Ala Gly Cys Cys Gly Gly Cys Cys Ala Cys Ala
2975 2980 2985

Gly Thr Cys Gly Ala Thr Gly Ala Ala Thr Cys Cys Ala Gly Ala
2990 2995 3000

Ala Ala Ala Gly Cys Gly Gly Cys Cys Ala Thr Thr Thr Cys
3005 3010 3015

Cys Ala Cys Cys Ala Thr Gly Ala Thr Ala Thr Thr Cys Gly Gly
3020 3025 3030

Cys Ala Ala Gly Cys Ala Gly Gly Cys Ala Thr Cys Gly Cys Cys
3035 3040 3045

Ala Thr Gly Ala Gly Thr Cys Ala Cys Gly Ala Cys Gly Ala Gly
3050 3055 3060

Ala Thr Cys Cys Thr Cys Gly Cys Cys Gly Thr Cys Gly Gly Gly
3065 3070 3075

Cys Ala Thr Gly Cys Gly Cys Gly Cys Cys Thr Thr Gly Ala Gly
3080 3085 3090

Cys Cys Thr Gly Gly Cys Gly Ala Ala Cys Ala Gly Thr Thr Cys
3095 3100 3105

Gly Gly Cys Thr Gly Gly Cys Gly Cys Gly Ala Gly Cys Cys Cys
3110 3115 3120

Cys Thr Gly Ala Thr Gly Cys Thr Cys Thr Cys Gly Thr Cys
3125 3130 3135

Cys Ala Gly Ala Thr Cys Ala Thr Cys Cys Thr Gly Ala Thr Cys
3140 3145 3150

Gly Ala Cys Ala Ala Gly Ala Cys Cys Gly Gly Cys Thr Thr Cys
3155 3160 3165

Cys Ala Thr Cys Cys Gly Ala Gly Thr Ala Cys Gly Thr Gly Cys
3170 3175 3180

Thr Cys Gly Cys Thr Cys Gly Ala Thr Gly Cys Gly Ala Thr Gly
3185 3190 3195

A-743 PCT.ST25.txt

Thr Thr Thr Cys Gly Cys Thr Thr Gly Gly Thr Gly Gly Thr Cys
3200 3205 3210

Gly Ala Ala Thr Gly Gly Cys Ala Gly Gly Thr Ala Gly Cys
3215 3220 3225

Cys Gly Gly Ala Thr Cys Ala Ala Gly Cys Gly Thr Ala Thr Gly
3230 3235 3240

Cys Ala Gly Cys Cys Gly Cys Cys Gly Cys Ala Thr Thr Gly Cys
3245 3250 3255

Ala Thr Cys Ala Gly Cys Cys Ala Thr Gly Ala Thr Gly Gly Ala
3260 3265 3270

Thr Ala Cys Thr Thr Thr Cys Thr Cys Gly Gly Cys Ala Gly Gly
3275 3280 3285

Ala Gly Cys Ala Ala Gly Gly Thr Gly Ala Gly Ala Thr Gly Ala
3290 3295 3300

Cys Ala Gly Gly Ala Gly Ala Thr Cys Cys Thr Gly Cys Cys Cys
3305 3310 3315

Cys Gly Gly Cys Ala Cys Thr Thr Cys Gly Cys Cys Cys Ala Ala
3320 3325 3330

Thr Ala Gly Cys Ala Gly Cys Cys Ala Gly Thr Cys Cys Cys Thr
3335 3340 3345

Thr Cys Cys Cys Gly Cys Thr Thr Cys Ala Gly Thr Gly Ala Cys
3350 3355 3360

Ala Ala Cys Gly Thr Cys Gly Ala Gly Cys Ala Cys Ala Gly Cys
3365 3370 3375

Thr Gly Cys Gly Cys Ala Ala Gly Gly Ala Ala Cys Gly Cys Cys
3380 3385 3390

Cys Gly Thr Cys Gly Thr Gly Gly Cys Cys Ala Gly Cys Cys Ala
3395 3400 3405

Cys Gly Ala Thr Ala Gly Cys Cys Gly Cys Gly Cys Thr Gly Cys
3410 3415 3420

Cys Thr Cys Gly Thr Cys Cys Thr Gly Cys Ala Ala Thr Thr Cys
3425 3430 3435

Ala Thr Thr Cys Ala Gly Gly Ala Cys Ala Cys Cys Gly Gly Ala
3440 3445 3450

A-743 PCT.ST25.txt

Cys Ala Gly Gly Thr Cys Gly Gly Thr Cys Thr Thr Gly Ala Cys
3455 3460 3465

Ala Ala Ala Ala Ala Gly Ala Ala Cys Cys Gly Gly Gly Cys Gly
3470 3475 3480

Cys Cys Cys Cys Thr Gly Cys Gly Cys Thr Gly Ala Cys Ala Gly
3485 3490 3495

Cys Cys Gly Gly Ala Ala Cys Ala Cys Gly Gly Cys Gly Gly Cys
3500 3505 3510

Ala Thr Cys Ala Gly Ala Gly Cys Ala Gly Cys Cys Gly Ala Thr
3515 3520 3525

Thr Gly Thr Cys Thr Gly Thr Thr Gly Thr Gly Cys Cys Cys Ala
3530 3535 3540

Gly Thr Cys Ala Thr Ala Gly Cys Cys Gly Ala Ala Thr Ala Gly
3545 3550 3555

Cys Cys Thr Cys Thr Cys Cys Ala Cys Cys Cys Ala Ala Gly Cys
3560 3565 3570

Gly Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Cys Thr Gly Cys
3575 3580 3585

Gly Thr Gly Cys Ala Ala Thr Cys Cys Ala Thr Cys Cys Thr Thr Gly
3590 3595 3600

Thr Thr Cys Ala Ala Thr Cys Ala Thr Gly Cys Gly Ala Ala Ala
3605 3610 3615

Cys Gly Ala Thr Cys Cys Thr Cys Ala Thr Cys Cys Thr Gly Thr
3620 3625 3630

Cys Thr Cys Thr Thr Gly Ala Thr Cys Thr Gly Ala Thr Cys Thr
3635 3640 3645

Thr Gly Ala Thr Cys Cys Cys Cys Thr Gly Cys Gly Cys Cys Ala
3650 3655 3660

Thr Cys Ala Gly Ala Thr Cys Cys Thr Thr Gly Gly Cys Gly Gly
3665 3670 3675

Cys Ala Ala Gly Ala Ala Ala Gly Cys Cys Ala Thr Cys Cys Ala
3680 3685 3690

Gly Thr Thr Thr Ala Cys Thr Thr Thr Gly Cys Ala Gly Gly Gly
3695 3700 3705

A-743 PCT.ST25.txt

Cys Thr Thr Cys Cys Ala Ala Cys Cys Thr Thr Ala Cys Cys
 3710 3715 3720

Ala Gly Ala Gly Gly Cys Gly Cys Cys Cys Cys Ala Gly Cys
 3725 3730 3735

Thr Gly Gly Cys Ala Ala Thr Thr Cys Cys Gly Gly Thr Thr Cys
 3740 3745 3750

Gly Cys Thr Thr Gly Cys Thr Gly Thr Cys Cys Ala Thr Ala Ala
 3755 3760 3765

Ala Ala Cys Cys Gly Cys Cys Cys Ala Gly Thr Cys Thr Ala Gly
 3770 3775 3780

Cys Thr Ala Thr Cys Gly Cys Cys Ala Thr Gly Thr Ala Ala Gly
 3785 3790 3795

Cys Cys Cys Ala Cys Thr Gly Cys Ala Ala Gly Cys Thr Ala Cys
 3800 3805 3810

Cys Thr Gly Cys Thr Thr Cys Thr Cys Thr Thr Gly Cys
 3815 3820 3825

Gly Cys Thr Thr Gly Cys Gly Thr Thr Thr Thr Cys Cys Cys Thr
 3830 3835 3840

Thr Gly Thr Cys Cys Ala Gly Ala Thr Ala Gly Cys Cys Cys Ala
 3845 3850 3855

Gly Thr Ala Gly Cys Thr Gly Ala Cys Ala Thr Thr Cys Ala Thr
 3860 3865 3870

Cys Cys Gly Gly Gly Thr Cys Ala Gly Cys Ala Cys Cys Gly
 3875 3880 3885

Thr Thr Thr Cys Thr Gly Cys Gly Gly Ala Cys Thr Gly Gly Cys
 3890 3895 3900

Thr Thr Thr Cys Thr Ala Cys Gly Thr Gly Thr Thr Cys Cys Gly
 3905 3910 3915

Cys Thr Thr Cys Cys Thr Thr Thr Ala Gly Cys Ala Gly Cys Cys
 3920 3925 3930

Cys Thr Thr Gly Cys Gly Cys Cys Thr Gly Ala Gly Thr Gly
 3935 3940 3945

Cys Thr Thr Gly Cys Gly Cys Ala Gly Cys Gly Thr Gly Ala
 3950 3955 3960

A-743 PCT.ST25.txt

Ala Gly Cys Thr Ala Cys Ala Thr Ala Thr Ala Thr Gly Thr Gly
3965 3970 3975

Ala Thr Cys Cys Gly Gly Cys Ala Ala Ala Thr Cys Gly Cys
3980 3985 3990

Thr Gly Ala Ala Thr Ala Thr Thr Cys Cys Thr Thr Thr Gly
3995 4000 4005

Thr Cys Thr Cys Cys Gly Ala Cys Cys Ala Thr Cys Ala Gly Gly
4010 4015 4020

Cys Ala Cys Cys Thr Gly Ala Gly Thr Cys Gly Cys Thr Gly Thr
4025 4030 4035

Cys Thr Thr Thr Thr Cys Gly Thr Gly Ala Cys Ala Thr Thr
4040 4045 4050

Cys Ala Gly Thr Thr Cys Gly Cys Thr Gly Cys Gly Cys Thr Cys
4055 4060 4065

Ala Cys Gly Gly Cys Thr Cys Thr Gly Gly Cys Ala Gly Thr Gly
4070 4075 4080

Ala Ala Thr Gly Gly Gly Thr Ala Ala Ala Thr Gly Gly
4085 4090 4095

Cys Ala Cys Thr Ala Cys Ala Gly Gly Cys Gly Cys Cys Thr Thr
4100 4105 4110

Thr Thr Ala Thr Gly Ala Thr Thr Cys Ala Thr Gly Cys Ala
4115 4120 4125

Ala Gly Gly Ala Ala Ala Cys Thr Ala Cys Cys Cys Ala Thr Ala
4130 4135 4140

Ala Thr Ala Cys Ala Ala Gly Ala Ala Ala Ala Gly Cys Cys Cys
4145 4150 4155

Gly Thr Cys Ala Cys Gly Gly Cys Thr Thr Cys Thr Cys Ala
4160 4165 4170

Gly Gly Gly Cys Gly Thr Thr Thr Ala Thr Gly Gly Cys Gly
4175 4180 4185

Gly Gly Thr Cys Thr Gly Cys Thr Ala Thr Gly Thr Gly Gly Thr
4190 4195 4200

Gly Cys Thr Ala Thr Cys Thr Gly Ala Cys Thr Thr Thr Thr
4205 4210 4215

A-743 PCT.ST25.txt

Gly Cys Thr Gly Thr Thr Cys Ala Gly Cys Ala Gly Thr Thr Cys
4220 4225 4230

Cys Thr Gly Cys Cys Cys Thr Cys Thr Gly Ala Thr Thr Thr Thr
4235 4240 4245

Cys Cys Ala Gly Thr Cys Thr Gly Ala Cys Cys Ala Cys Thr Thr
4250 4255 4260

Cys Gly Gly Ala Thr Thr Ala Thr Cys Cys Cys Gly Thr Gly Ala
4265 4270 4275

Cys Ala Gly Gly Thr Cys Ala Thr Thr Cys Ala Gly Ala Cys Thr
4280 4285 4290

Gly Gly Cys Thr Ala Ala Thr Gly Cys Ala Cys Cys Cys Ala Gly
4295 4300 4305

Thr Ala Ala Gly Gly Cys Ala Gly Cys Gly Gly Thr Ala Thr Cys
4310 4315 4320

Ala Thr Cys Ala Ala Cys Ala Gly Gly Cys Thr Thr Ala Cys Cys
4325 4330 4335

Cys Gly Thr Cys Thr Thr Ala Cys Thr Gly Thr Cys Gly Ala Ala
4340 4345 4350

Gly Ala Cys Gly Thr Gly Cys Gly Thr Ala Ala Cys Gly Thr Ala
4355 4360 4365

Thr Gly Cys Ala Thr Gly Gly Thr Cys Thr Cys Cys Cys Ala
4370 4375 4380

Thr Gly Cys Gly Ala Gly Ala Gly Thr Ala Gly Gly Gly Ala Ala
4385 4390 4395

Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys Ala Ala Ala
4400 4405 4410

Thr Ala Ala Ala Ala Cys Gly Ala Ala Ala Gly Gly Cys Thr Cys
4415 4420 4425

Ala Gly Thr Cys Gly Ala Ala Ala Gly Ala Cys Thr Gly Gly Gly
4430 4435 4440

Cys Cys Thr Thr Thr Cys Gly Thr Thr Thr Thr Ala Thr Cys Thr
4445 4450 4455

Gly Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Gly Thr Gly Ala
4460 4465 4470

A-743 PCT.ST25.txt

Ala Cys Gly Cys Thr Cys Thr Cys Cys Thr Gly Ala Gly Thr Ala
4475 4480 4485

Gly Gly Ala Cys Ala Ala Ala Thr Cys Cys Gly Cys Cys Gly Gly
4490 4495 4500

Gly Ala Gly Cys Gly Gly Ala Thr Thr Thr Gly Ala Ala Cys Gly
4505 4510 4515

Thr Thr Gly Cys Gly Ala Ala Gly Cys Ala Ala Cys Gly Gly Cys
4520 4525 4530

Cys Cys Gly Gly Ala Gly Gly Gly Thr Gly Gly Cys Gly Gly Gly
4535 4540 4545

Cys Ala Gly Gly Ala Cys Gly Cys Cys Cys Gly Cys Cys Ala Thr
4550 4555 4560

Ala Ala Ala Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Thr Cys
4565 4570 4575

Ala Ala Ala Thr Thr Ala Ala Gly Cys Ala Gly Ala Ala Gly Gly
4580 4585 4590

Cys Cys Ala Thr Cys Cys Thr Gly Ala Cys Gly Gly Ala Thr Gly
4595 4600 4605

Gly Cys Cys Thr Thr Thr Thr Thr Gly Cys Gly Thr Thr Thr Cys
4610 4615 4620

Thr Ala Cys Ala Ala Ala Cys Thr Cys Thr Thr Thr Thr Gly Thr
4625 4630 4635

Thr Thr Ala Thr Thr Thr Thr Cys Thr Ala Ala Ala Thr Ala
4640 4645 4650

Cys Ala Thr Thr Cys Ala Ala Ala Thr Ala Thr Gly Gly Ala Cys
4655 4660 4665

Gly Thr Cys Gly Thr Ala Cys Thr Thr Ala Ala Cys Thr Thr Thr
4670 4675 4680

Thr Ala Ala Ala Gly Thr Ala Thr Gly Gly Gly Cys Ala Ala Thr
4685 4690 4695

Cys Ala Ala Thr Thr Gly Cys Thr Cys Cys Thr Gly Thr Thr Ala
4700 4705 4710

Ala Ala Ala Thr Thr Gly Cys Thr Thr Thr Ala Gly Ala Ala Ala
4715 4720 4725

A-743 PCT.ST25.txt

Thr Ala Cys Thr Thr Thr Gly Gly Cys Ala Gly Cys Gly Gly Thr
4730 4735 4740

Thr Thr Gly Thr Thr Gly Thr Ala Thr Thr Gly Ala Gly Thr Thr
4745 4750 4755

Thr Cys Ala Thr Thr Thr Gly Cys Gly Cys Ala Thr Thr Gly Gly
4760 4765 4770

Thr Thr Ala Ala Ala Thr Gly Gly Ala Ala Ala Gly Thr Gly Ala
4775 4780 4785

Cys Cys Gly Thr Gly Cys Gly Cys Thr Thr Ala Cys Thr Ala Cys
4790 4795 4800

Ala Gly Cys Cys Thr Ala Ala Thr Ala Thr Thr Thr Thr Gly
4805 4810 4815

Ala Ala Ala Thr Ala Thr Cys Cys Cys Ala Ala Gly Ala Gly Cys
4820 4825 4830

Thr Thr Thr Thr Cys Cys Thr Thr Cys Gly Cys Ala Thr Gly
4835 4840 4845

Cys Cys Cys Ala Cys Gly Cys Thr Ala Ala Ala Cys Ala Thr Thr
4850 4855 4860

Cys Thr Thr Thr Thr Cys Thr Cys Thr Thr Thr Gly Gly
4865 4870 4875

Thr Thr Ala Ala Ala Thr Cys Gly Thr Thr Gly Thr Thr Gly
4880 4885 4890

Ala Thr Thr Thr Ala Thr Thr Ala Thr Thr Thr Gly Cys Thr Ala
4895 4900 4905

Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Cys Gly Ala Thr
4910 4915 4920

Ala Ala Thr Thr Ala Thr Cys Ala Ala Cys Thr Ala Gly Ala Gly
4925 4930 4935

Ala Ala Gly Gly Ala Ala Cys Ala Ala Thr Thr Ala Ala Thr Gly
4940 4945 4950

Gly Thr Ala Thr Gly Thr Thr Cys Ala Thr Ala Cys Ala Cys Gly
4955 4960 4965

Cys Ala Thr Gly Thr Ala Ala Ala Ala Ala Thr Ala Ala Ala Cys
4970 4975 4980

A-743 PCT.ST25.txt

Thr Ala Thr Cys Thr Ala Thr Ala Thr Ala Gly Thr Thr Gly Thr
4985 4990 4995

Cys Thr Thr Thr Cys Thr Cys Thr Gly Ala Ala Thr Gly Thr Gly
5000 5005 5010

Cys Ala Ala Ala Ala Cys Thr Ala Ala Gly Cys Ala Thr Thr Cys
5015 5020 5025

Cys Gly Ala Ala Gly Cys Cys Ala Thr Thr Ala Thr Thr Ala Gly
5030 5035 5040

Cys Ala Gly Thr Ala Thr Gly Ala Ala Thr Ala Gly Gly Gly Ala
5045 5050 5055

Ala Ala Cys Thr Ala Ala Ala Cys Cys Cys Ala Gly Thr Gly Ala
5060 5065 5070

Thr Ala Ala Gly Ala Cys Cys Thr Gly Ala Thr Gly Ala Thr Thr
5075 5080 5085

Thr Cys Gly Cys Thr Thr Cys Thr Thr Thr Ala Ala Thr Thr Ala
5090 5095 5100

Cys Ala Thr Thr Thr Gly Gly Ala Gly Ala Thr Thr Thr Thr Thr
5105 5110 5115

Thr Ala Thr Thr Thr Ala Cys Ala Gly Cys Ala Thr Thr Gly Thr
5120 5125 5130

Thr Thr Thr Cys Ala Ala Ala Thr Ala Thr Ala Thr Thr Cys Cys
5135 5140 5145

Ala Ala Thr Thr Ala Ala Thr Cys Gly Gly Thr Gly Ala Ala Thr
5150 5155 5160

Gly Ala Thr Thr Gly Gly Ala Gly Thr Thr Ala Gly Ala Ala Thr
5165 5170 5175

Ala Ala Thr Cys Thr Ala Cys Thr Ala Thr Ala Gly Gly Ala Thr
5180 5185 5190

Cys Ala Thr Ala Thr Thr Thr Ala Thr Thr Ala Ala Ala Thr
5195 5200 5205

Thr Ala Gly Cys Gly Thr Cys Ala Thr Cys Ala Thr Ala Ala Thr
5210 5215 5220

Ala Thr Thr Gly Cys Cys Thr Cys Cys Ala Thr Thr Thr Thr Thr
5225 5230 5235

A-743 PCT.ST25.txt

Thr Ala Gly Gly Gly Thr Ala Ala Thr Thr Ala Thr Cys Cys Ala
5240 5245 5250

Gly Ala Ala Thr Thr Gly Ala Ala Ala Thr Ala Thr Cys Ala Gly
5255 5260 5265

Ala Thr Thr Thr Ala Ala Cys Cys Ala Thr Ala Gly Ala Ala Thr
5270 5275 5280

Gly Ala Gly Gly Ala Thr Ala Ala Ala Thr Gly Ala Thr Cys Gly
5285 5290 5295

Cys Gly Ala Gly Thr Ala Ala Ala Thr Ala Ala Thr Ala Thr Thr
5300 5305 5310

Cys Ala Cys Ala Ala Thr Gly Thr Ala Cys Cys Ala Thr Thr Thr
5315 5320 5325

Thr Ala Gly Thr Cys Ala Thr Ala Thr Cys Ala Gly Ala Thr Ala
5330 5335 5340

Ala Gly Cys Ala Thr Thr Gly Ala Thr Thr Ala Ala Thr Ala Thr
5345 5350 5355

Cys Ala Thr Thr Ala Thr Thr Gly Cys Thr Thr Cys Thr Ala Cys
5360 5365 5370

Ala Gly Gly Cys Thr Thr Thr Ala Ala Thr Thr Thr Thr Ala Thr
5375 5380 5385

Thr Ala Ala Thr Thr Ala Thr Thr Cys Thr Gly Thr Ala Ala Gly
5390 5395 5400

Thr Gly Thr Cys Gly Thr Cys Gly Gly Cys Ala Thr Thr Thr Ala
5405 5410 5415

Thr Gly Thr Cys Thr Thr Thr Cys Ala Thr Ala Cys Cys Cys Ala
5420 5425 5430

Thr Cys Thr Cys Thr Thr Thr Ala Thr Cys Cys Thr Thr Ala Cys
5435 5440 5445

Cys Thr Ala Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Cys Ala
5450 5455 5460

Ala Gly Thr Thr Thr Thr Gly Cys Gly Thr Gly Thr Thr Ala Thr
5465 5470 5475

Ala Thr Ala Thr Cys Ala Thr Thr Ala Ala Ala Ala Cys Gly Gly
5480 5485 5490

A-743 PCT.ST25.txt

Thr Ala Ala Thr Ala Gly Ala Thr Thr Gly Ala Cys Ala Thr Thr
5495 5500 5505

Thr Gly Ala Thr Thr Cys Thr Ala Ala Thr Ala Ala Ala Thr Thr
5510 5515 5520

Gly Gly Ala Thr Thr Thr Thr Gly Thr Cys Ala Cys Ala Cys
5525 5530 5535

Thr Ala Thr Thr Ala Thr Ala Thr Cys Gly Cys Thr Thr Gly Ala
5540 5545 5550

Ala Ala Thr Ala Cys Ala Ala Thr Thr Gly Thr Thr Thr Ala Ala
5555 5560 5565

Cys Ala Thr Ala Ala Gly Thr Ala Cys Cys Thr Gly Thr Ala Gly
5570 5575 5580

Gly Ala Thr Cys Gly Thr Ala Cys Ala Gly Gly Thr Thr Ala
5585 5590 5595

Cys Gly Cys Ala Ala Gly Ala Ala Ala Ala Thr Gly Gly Thr Thr
5600 5605 5610

Thr Gly Thr Thr Ala Thr Ala Gly Thr Cys Gly Ala Thr Thr Ala
5615 5620 5625

Ala Thr Cys Gly Ala Thr Thr Gly Ala Thr Thr Cys Thr Ala
5630 5635 5640

Gly Ala Thr Thr Thr Gly Thr Thr Thr Ala Ala Cys Thr Ala
5645 5650 5655

Ala Thr Thr Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Thr Ala
5660 5665 5670

Ala Cys Ala Thr Ala Thr Gly Ala Thr Cys Gly Cys Thr Cys Cys
5675 5680 5685

Ala Cys Cys Ala Thr Gly Cys Ala Cys Cys Ala Gly Thr Gly Ala
5690 5695 5700

Gly Ala Ala Gly Cys Ala Thr Thr Ala Thr Gly Ala Gly Cys Ala
5705 5710 5715

Thr Cys Thr Gly Gly Ala Cys Gly Gly Thr Gly Cys Thr Gly
5720 5725 5730

Thr Ala Ala Cys Ala Ala Ala Thr Gly Thr Gly Ala Ala Cys Cys
5735 5740 5745

A-743 PCT.ST25.txt

Ala Gly Gly Ala Ala Ala Gly Thr Ala Cys Ala Thr Gly Thr Cys
5750 5755 5760

Thr Thr Cys Thr Ala Ala Ala Thr Gly Cys Ala Cys Thr Ala Cys
5765 5770 5775

Thr Ala Cys Cys Thr Cys Thr Gly Ala Cys Ala Gly Thr Gly Thr
5780 5785 5790

Ala Thr Gly Thr Cys Thr Gly Cys Cys Cys Thr Gly Thr Gly Gly
5795 5800 5805

Cys Cys Cys Gly Gly Ala Thr Gly Ala Ala Thr Ala Cys Thr Thr
5810 5815 5820

Gly Gly Ala Thr Ala Gly Cys Thr Gly Gly Ala Ala Thr Gly Ala
5825 5830 5835

Ala Gly Ala Ala Gly Ala Thr Ala Ala Ala Thr Gly Cys Thr Thr
5840 5845 5850

Gly Cys Thr Gly Cys Ala Thr Ala Ala Ala Gly Thr Thr Thr Gly
5855 5860 5865

Thr Gly Ala Thr Ala Cys Ala Gly Gly Cys Ala Ala Gly Gly Cys
5870 5875 5880

Cys Cys Thr Gly Gly Thr Gly Gly Cys Cys Gly Thr Gly Gly Thr
5885 5890 5895

Cys Gly Cys Cys Gly Gly Cys Ala Ala Cys Ala Gly Thr Ala Cys
5900 5905 5910

Gly Ala Cys Cys Cys Cys Cys Cys Gly Gly Cys Gly Cys Thr Gly
5915 5920 5925

Cys Gly Cys Gly Thr Gly Cys Ala Cys Gly Gly Cys Thr Gly Gly
5930 5935 5940

Gly Thr Ala Cys Cys Ala Cys Thr Gly Gly Ala Gly Cys Cys Ala
5945 5950 5955

Gly Gly Ala Cys Thr Gly Cys Gly Ala Gly Thr Gly Cys Thr Gly
5960 5965 5970

Cys Cys Gly Cys Cys Gly Cys Ala Ala Cys Ala Cys Cys Gly Ala
5975 5980 5985

Gly Thr Gly Cys Gly Cys Gly Cys Cys Gly Gly Cys Cys Thr
5990 5995 6000

A-743 PCT.ST25.txt

Gly Gly Gly Cys Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Cys
6005 6010 6015

Gly Thr Thr Gly Cys Ala Gly Cys Thr Cys Ala Ala Cys Ala Ala
6020 6025 6030

Gly Gly Ala Cys Ala Cys Ala Gly Thr Gly Thr Gly Cys Ala Ala
6035 6040 6045

Ala Cys Cys Thr Thr Gly Cys Cys Thr Thr Gly Cys Ala Gly Gly
6050 6055 6060

Cys Thr Ala Cys Thr Thr Cys Cys Thr Cys Thr Gly Ala Thr Gly Cys
6065 6070 6075

Cys Thr Thr Thr Cys Cys Thr Cys Cys Ala Cys Gly Gly Ala
6080 6085 6090

Cys Ala Ala Ala Thr Gly Cys Ala Gly Ala Cys Cys Cys Thr Gly
6095 6100 6105

Gly Ala Cys Cys Ala Ala Cys Thr Gly Thr Ala Cys Cys Thr Thr
6110 6115 6120

Cys Cys Thr Thr Gly Gly Ala Ala Ala Gly Ala Gly Thr
6125 6130 6135

Ala Gly Ala Ala Cys Ala Thr Cys Ala Thr Gly Gly Ala Cys
6140 6145 6150

Ala Gly Ala Gly Ala Ala Ala Thr Cys Cys Gly Ala Thr Gly Thr
6155 6160 6165

Gly Gly Thr Thr Thr Gly Cys Ala Gly Thr Thr Cys Thr Thr Cys
6170 6175 6180

Thr Cys Thr Gly Cys Cys Ala Gly Cys Thr Ala Gly Ala Ala Ala
6185 6190 6195

Ala Cys Cys Ala Cys Cys Ala Ala Ala Thr Gly Ala Ala Cys Cys
6200 6205 6210

Cys Cys Ala Thr Gly Thr Thr Ala Cys Gly Thr Cys Gly Ala
6215 6220 6225

Cys Ala Ala Ala Ala Cys Thr Cys Ala Cys Ala Cys Ala Thr Gly
6230 6235 6240

Thr Cys Cys Ala Cys Cys Thr Thr Gly Thr Cys Cys Ala Gly Cys
6245 6250 6255

A-743 PCT.ST25.txt

Thr Cys Cys Gly Gly Ala Ala Cys Thr Cys Cys Thr Gly Gly Gly
6260 6265 6270

Gly Gly Gly Ala Cys Cys Gly Thr Cys Ala Gly Thr Cys Thr Thr
6275 6280 6285

Cys Cys Thr Cys Thr Cys Cys Cys Cys Cys Ala Ala Ala
6290 6295 6300

Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys Ala Cys Cys Cys Thr
6305 6310 6315

Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys Gly Gly Ala Cys
6320 6325 6330

Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys Ala Thr Gly
6335 6340 6345

Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys Gly Thr
6350 6355 6360

Gly Ala Gly Cys Cys Ala Cys Gly Ala Ala Gly Ala Cys Cys Cys
6365 6370 6375

Thr Gly Ala Gly Gly Thr Cys Ala Ala Gly Thr Thr Cys Ala Ala
6380 6385 6390

Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly
6395 6400 6405

Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala
6410 6415 6420

Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Gly Cys Cys
6425 6430 6435

Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Ala
6440 6445 6450

Cys Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly
6455 6460 6465

Thr Gly Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr
6470 6475 6480

Cys Ala Cys Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala
6485 6490 6495

Gly Gly Ala Cys Thr Gly Gly Cys Thr Gly Ala Ala Thr Gly Gly
6500 6505 6510

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Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly
6515 6520 6525

Cys Ala Ala Gly Gly Thr Cys Thr Cys Cys Ala Ala Cys Ala Ala
6530 6535 6540

Ala Gly Cys Cys Cys Thr Cys Cys Cys Ala Gly Cys Cys Cys Cys
6545 6550 6555

Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala Cys Cys Ala Thr
6560 6565 6570

Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly
6575 6580 6585

Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala Cys Cys
6590 6595 6600

Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys Thr
6605 6610 6615

Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala
6620 6625 6630

Thr Gly Ala Gly Cys Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala
6635 6640 6645

Cys Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys
6650 6655 6660

Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly
6665 6670 6675

Cys Thr Thr Cys Thr Ala Thr Cys Cys Cys Ala Gly Cys Gly Ala
6680 6685 6690

Cys Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly
6695 6700 6705

Gly Gly Ala Gly Ala Gly Cys Ala Ala Thr Gly Gly Cys Ala
6710 6715 6720

Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Ala Ala Cys Thr Ala
6725 6730 6735

Cys Ala Ala Gly Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys
6740 6745 6750

Cys Gly Thr Gly Cys Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala
6755 6760 6765

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Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys Cys Thr
6770 6775 6780

Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly Cys Thr Cys Ala Cys
6785 6790 6795

Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly
6800 6805 6810

Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly Ala Ala
6815 6820 6825

Cys Gly Thr Cys Thr Cys Thr Cys Thr Cys Ala Thr Gly Cys Thr Cys
6830 6835 6840

Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly Cys
6845 6850 6855

Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala
6860 6865 6870

Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr
6875 6880 6885

Cys Thr Cys Cys Cys Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly
6890 6895 6900

Thr Ala Ala Ala Thr Ala Ala Thr Gly Gly Ala Thr Cys Cys Gly
6905 6910 6915

Cys Gly Gly Ala Ala Ala Gly Ala Ala Gly Ala Ala Gly Ala Ala
6920 6925 6930

Gly Ala Ala Gly Ala Ala Gly Ala Ala Ala Gly Cys Cys Cys Gly
6935 6940 6945

Ala Ala Ala Gly Gly Ala Ala Gly Cys Thr Gly Ala Gly Thr Thr
6950 6955 6960

Gly Gly Cys Thr Gly Cys Thr Gly Cys Cys Ala Cys Cys Gly Cys
6965 6970 6975

Thr Gly Ala Gly Cys Ala Ala Thr Ala Ala Cys Thr Ala Gly Cys
6980 6985 6990

Ala Thr Ala Ala Cys Cys Cys Cys Thr Thr Gly Gly Gly Gly Cys
6995 7000 7005

Cys Thr Cys Thr Ala Ala Ala Cys Gly Gly Gly Thr Cys Thr Thr
7010 7015 7020

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Gly Ala Gly Gly Gly Thr Thr Thr Thr Thr Thr Gly Cys Thr
7025 7030 7035

Gly Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Cys Cys Gly Cys
7040 7045 7050 7055

Thr Cys Thr Thr Cys Ala Cys Gly Cys Thr Cys Thr Cys Ala
7055 7060 7065

Cys Gly Cys Gly Gly Ala Thr Ala Ala Ala Thr Ala Ala Gly Thr
7070 7075 7080

Ala Ala Cys Gly Ala Thr Cys Cys Gly Gly Thr Cys Cys Ala Gly
7085 7090 7095

Thr Ala Ala Thr Gly Ala Cys Cys Thr Cys Ala Gly Ala Ala Cys
7100 7105 7110

Thr Cys Cys Ala Thr Cys Thr Gly Gly Ala Thr Thr Thr Gly Thr
7115 7120 7125

Thr Cys Ala Gly Ala Ala Cys Gly Cys Thr Cys Gly Gly Thr Thr
7130 7135 7140

Gly Cys Cys Gly Cys Cys Gly Gly Gly Cys Gly Thr Thr Thr Thr
7145 7150 7155

Thr Thr Ala Thr Thr Gly Gly Thr Gly Ala Gly Ala Ala Thr Cys
7160 7165 7170

Gly Cys Ala Gly Cys Ala Ala Cys Thr Thr Gly Thr Cys Gly Cys
7175 7180 7185

Gly Cys Cys Ala Ala Thr Cys Gly Ala Gly Cys Cys Ala Thr Gly
7190 7195 7200

Thr Cys Gly Thr Cys Gly Thr Cys Ala Ala Cys Gly Ala Cys Cys
7205 7210 7215

Cys Cys Cys Cys Ala Thr Thr Cys Ala Ala Gly Ala Ala Cys Ala
7220 7225 7230

Gly Cys Ala Ala Gly Cys Ala Gly Cys Ala Thr Thr Gly Ala Gly
7235 7240 7245

Ala Ala Cys Thr Thr Thr Gly Gly Ala Ala Thr Cys Cys Ala Gly
7250 7255 7260

Thr Cys Cys Cys Thr Cys Thr Thr Cys Cys Ala Cys Cys Thr Gly
7265 7270 7275

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Cys Thr Gly Ala Cys Cys Gly
7280 7285

<210> 29
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 29

Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala
1 5 10

<210> 30
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 30

Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu
1 5 10

<210> 31
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 31

Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala
1 5 10

<210> 32
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 32

Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys Phe
1 5 10 15

His His

<210> 33
<211> 18
<212> PRT

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<213> Artificial Sequence

<220>

<223> Preferred TALL-1 Modulating Domains

<400> 33

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu

<210> 34

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 Modulating Domains

<400> 34

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser

<210> 35

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 Modulating Domains

<400> 35

Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys Ser
1 5 10 15

Asn Leu

<210> 36

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 Modulating Domains

<400> 36

Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys Gln
1 5 10 15

Phe Asn

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<210> 37
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains
<400> 37

Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys His
1 5 10 15

Gly Leu

<210> 38
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains
<400> 38

Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys Pro
1 5 10 15

Ser Pro

<210> 39
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains
<400> 39

Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys Glu
1 5 10 15

Phe Phe

<210> 40
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 40
gggkgggg

<210> 41

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<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<220>
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<222> (4)..(4)
<223> N is asparagine

<400> 41
gggnngsgg

8

<210> 42
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 42
gggcgggg

8

<210> 43
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 43

Gly Pro Asn Gly Gly
1 5

<210> 44
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 44

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Xaa

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<210> 45
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 45

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu

<210> 46
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (38)..(38)
<223> Xaa = a peptide bond
Fc domain attached at Position 38 to C-terminus

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<400> 46

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp
20 25 30

Val Cys Asp Pro Leu Xaa
35

<210> 47
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

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<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (20)..(20)
<223> Xaa = a peptide bond

<400> 47

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln
20 25 30

Trp Val Cys Asp Pro Leu
35

<210> 48
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 48

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser Xaa

<210> 49
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 49

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Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
1 5 10 15

Thr Ser Ser

<210> 50
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (36)..(36)
<223> Xaa = a peptide bond
Fc domain attached at Position 36 to C-terminus

<220>
<221> misc_feature
<222> (18)..(18)
<223> Xaa = a peptide bond

<400> 50

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser
1 5 10 15

Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val
20 25 30

Thr Ser Ser Xaa
35

<210> 51
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<400> 51

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr
Page 49

1 5 10 15

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Ser Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp
20 25 30

Val Thr Ser Ser
35

<210> 52
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 52

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Xaa

<210> 53
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 53

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu

<210> 54
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

A-743 PCT.ST25.txt

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<220>
<221> misc_feature
<222> (38)..(38)
<223> Xaa = a peptide bond
Fc domain attached at Position 38 to C-terminus

<400> 54

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp
20 25 30

Val Cys His Gly Leu Xaa
35

<210> 55
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (20)..(20)
<223> Xaa = a peptide bond

<400> 55

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln
20 25 30

Trp Val Cys His Gly Leu
35

<210> 56
<211> 25
<212> DNA
<213> Artificial Sequence

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<220>
<223> Oligonucleotide

<400> 56
cggcgcaact atcggtatca agctg

25

<210> 57
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 57
catgtaccgt aacactgagt ttccgtc

26

<210> 58
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus peptide

<400> 58

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu

<210> 59
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred linker sequence

<400> 59

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1 5 10 15

Ser Gly Ser Ala Thr His Met
20

<210> 60
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 60

Asn Gln Thr Leu Trp Lys Trp Asp Leu Leu Thr Lys Gln Phe Ile Thr
1 5 10 15

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Tyr Met

<210> 61
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 61

Pro Val Tyr Gln Gly Trp Trp Asp Thr Leu Thr Lys Leu Tyr Ile Trp
1 5 10 15

Asp Gly

<210> 62
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 62

Trp Leu Asp Gly Gly Trp Arg Asp Pro Leu Ile Lys Arg Ser Val Gln
1 5 10 15

Leu Gly

<210> 63
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 63

Gly His Gln Gln Phe Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Ser Asn

<210> 64
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 64

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Gln Arg Val Gly Gln Phe Trp Asp Val Leu Thr Lys Met Phe Ile Thr
1 5 10 15

Gly Ser

<210> 65
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 65

Gln Ala Gln Gly Trp Ser Tyr Asp Ala Leu Ile Lys Thr Trp Ile Arg
1 5 10 15

Trp Pro

<210> 66
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 66

Gly Trp Met His Trp Lys Trp Asp Pro Leu Thr Lys Gln Ala Leu Pro
1 5 10 15

Trp Met

<210> 67
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 67

Gly His Pro Thr Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Leu
1 5 10 15

Gln Met

<210> 68
<211> 18
<212> PRT
<213> Artificial Sequence

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<220>
<223> Preferred TALL-1 modulating domains

<400> 68

Trp Asn Asn Trp Ser Leu Trp Asp Pro Leu Thr Lys Leu Trp Leu Gln
1 5 10 15

Gln Asn

<210> 69
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 69

Trp Gln Trp Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Gln Gln

<210> 70
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 70

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Thr Lys Met Trp Leu Gly
1 5 10 15

Thr Ser

<210> 71
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 71
tatgccgggt acttgtttcc cgttcccggt ggaatgcact cacgctggtg gaggcggtgg 60

gg 62

<210> 72
<211> 64
<212> DNA
<213> Artificial Sequence

A-743 PCT.ST25.txt

<220>
<223> Oligonucleotides

<400> 72
tcgaccccac cgcctcctgg agcgtgagtg cattcccacg ggaagccgaa acaagtaccc 60
ggca 64

<210> 73
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 73
tatgtgggt gcttgggc cgttccgtg ggaatgttc aaagaaggtg gaggcggtgg 60
gg 62

<210> 74
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 74
tcgaccccac cgcctccacc ttcttgaaa cattcccacg ggaacggcca acaagcaccc 60
caca 64

<210> 75
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 75
tatggttccg ttctgtgacc tgctgactaa acactgttgc gaagctggtg gaggcggtgg 60
gg 62

<210> 76
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 76
tcgaccccac cgcctccacc agttcgaaa cagtgttag tcagcaggc acagaacgga 60
acca 64

<210> 77
<211> 74
<212> DNA

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<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 77

tatgggttct cgttgtaaat acaaattggga cgttctgact aaacagtgtt tccaccacgg 60

tggaggcggt gggg

74

<210> 78

<211> 76

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 78

tcgaccccac cgccctccacc gtgggtggaaa cactgttttag tcagaacgac ccatttttat 60

ttacaacgag aaccca

76

<210> 79

<211> 74

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 79

tatgctggcg gggtgtaaat gggacctgct gatcaaacag tgggtttgtg acccgctggg 60

tggaggcggt gggg

74

<210> 80

<211> 76

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 80

tcgaccccac cgccctccacc cagcgggtca caaaccact gtttgcgtc caggtcccat 60

ttacaacccg gcagca

76

<210> 81

<211> 74

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotides

<400> 81

tatgtctgct gactgttact tcgacatcct gactaaatct gacgtttgtt cttttctgg 60

tggaggcggt gggg

74

<210> 82

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<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 82
tcgaccccac cgcctccacc agaagaagta caaacgtcag atttagtcag gatgtcgaag 60
taacagtca cagaca 76

<210> 83
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 83
tatgtctgac gactgtatgt acgaccagct gactcgtatg ttcatctgtt ctaacctggg 60
tggaggcggt gggg 74

<210> 84
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 84
tcgaccccac cgcctccacc caggttagaa cagatgaaca tacgagtcag ctggcgtac 60
atacagtctg cagaca 76

<210> 85
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 85
tatggacctg aactgtaaat acgacgaact gacttacaaa gaatgggtc agttcaacgg 60
tggaggcggt gggg 74

<210> 86
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 86
tcgaccccac cgcctccacc gttgaactga caccattctt tgtaagtcag ttgcgtat 60
ttacagttca ggtcca 76

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<210> 87
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 87
tatgttccac gactgtaaat acgacacctgct gactcgtag atggtttgc acggctctggg 60
tggaggcggt gggg 74

<210> 88
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 88
tcgaccacccac cgcctccacc cagaccgtga caaaccatct gacgagtcag caggcgtat 60
ttacagtcgt ggaaca 76

<210> 89
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 89
tatgcgtaac cactgtttct gggaccacct gctgaaacag gacatctgtc cgtctccggg 60
tggaggcggt gggg 74

<210> 90
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 90
tcgaccacccac cgcctccacc cggagacgga cagatgtcct gtttcagcag gtggtcccag 60
aaacagtggt tacgca 76

<210> 91
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 91
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tggaggcggt gggg

74

<210> 92
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 <213> Artificial Sequence

 <220>
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 caaacactggt tagcca 76

 <210> 93
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 <220>
 <223> Oligonucleotides

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 tggaggcggt gggg 74

 <210> 94
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 ttgcagtcgt ggaaca 76

 <210> 95
 <211> 141
 <212> DNA
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 <220>
 <223> pAMG21-RANK-Fc vector

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 tggcggtgat actgagcaca t 141

 <210> 96
 <211> 55
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> pAMG21-RANK-Fc vector

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<400> 96
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 ctcctgagta ggacaaatcc gccgggagcg gatttgaacg ttgcgaagca acggcccgga 180
 gggtggcggg caggacgccc gccataaaact gccaggcatc aaattaagca gaaggccatc 240
 ctgacggatg gccttttgc gtttctacaa actctttgt ttattttct aaatacatcc 300
 aaatatggac gtcgtactta acttttaaag tatgggcaat caattgtcc tggtaaaattt 360
 gcttagaaa tactttggca gcggttgtt gtattgagtt tcatttgcgc attggtaaa 420
 tggaaagtga ccgtgcgcctt actacagcct aatattttt aatataccca agagctttt 480
 ctttcgcattt cccacgctaa acattctttt tctctttgg ttaaatcggtt gtttgcattt 540
 ttatggcta tatttatttt tcgataattt tcaactagag aaggaacaat taatggatgt 600
 ttcatacacg catgaaaaaa taaactatct atatagttgt ctttctctga atgtcaaaa 660
 ctaagcattc cgaagccattt attagcagta tgaataggaa aactaaaccc agtgataaga 720
 cctgatgatt tcgcttcattt aattacattt ggagatttt tatttacagc attgtttca 780
 aatataattcc aattaatcgg tgaatgattt gagtttagat aatctactat aggatcatat 840
 tttattaaat tagcgtcatc ataattattgc ctccattttt tagggtaattt atccagaattt 900
 gaaatatcg atttaccat agaatgagga taaatgatcg cgagtaaata atattcacaa 960
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 aattgtttaa cataagtacc tgcaggatcg tacaggttta cgcaagaaaa tggtttgc 1260
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 tggtaacgc gttggaattc gagctcacta gtgtcgaccc gcagggtacc atgaaagctt 1380
 actcgaggat ccgcggaaag aagaagaaga agaagaaagc ccgaaaggaa gctgagttgg 1440
 ctgctgccac cgctgagcaa taactagcat aacccttgg ggcctctaaa cgggtcttgc 1500
 ggggtttttt gctgaaagga ggaaccgctc ttacgctct tcacgc 1546

<210> 98

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<211> 872
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<223> GM221

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gataatatat gagcacaaaaa aagaaaccat taacacaaga gcagctttag gacgcacg 180
gccttaaagc aatttatgaa aaaaagaaaa atgaacttgg cttatcccag gaatctgtcg 240
cagacaagat ggggatgggg cagtcaggcg ttggtgcttt attaatggc atcaatgcat 300
taaatgctta taacgcccga ttgcttacaa aaattctcaa agtttagcggtt gaagaattta 360
gcccttcaat cgccagagaa tctacgagat gtatgaagcg gtttagtatgc agccgtcact 420
tagaagttagtacccatgttttttc tcatgttcag gcagggatgt tctcacctaa 480
gcttagaacc tttaccaaag gtgatgcggaa gagatgggtaa agcacaacca aaaaagccag 540
tgattctgca ttctggcttg aggttgaagg taattccatg accgcaccaa caggctccaa 600
gccaagcttt cctgacggaa tgttaattct cgttgaccct gagcaggctg ttgagccagg 660
tgatttctgc atagccagac ttgggggtga ttagttagtacc ttcaagaaac tgatcaggaa 720
tagcgggtcag gtgttttac aaccactaaa cccacagtac ccaatgatcc catgcaatga 780
gagttgttcc gttgtgggaa aagttatcgc tagtcagtgg cctgaagaga cgtttggctg 840
atagactagt ggatccacta gtgtttctgc cc 872

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<210> 99
<211> 1197
<212> DNA
<213> Artificial Sequence

<220>
<223> GM221

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agtatgccgg tgtctttat cagaccgtt cccgcgtgg gaaccaggcc agccacgtt 180
ctgcgaaaac gcggggaaaaa gtcgaagcgg cgatggcgg a gctgaattac attcccaacc 240
gcgtggcaca acaactggcg ggcaaacagt cgctcctgat tggcgttgcc acctccagtc 300
tggccctgca cgcgccgtcg caaattgtcg cggcgattaa atctcgccgatcaactgg 360
gtgccagcgt ggtgggtcg atggtagaac gaagcggcgt cgaaggctgt aaagcggcgg 420
tgcacaatct tctcgccaa cgcgtcagtg ggctgatcat taactatccg ctggatgacc 480
aggatgccat tgctgtggaa gctgcctgca ctaatgttcc ggcgttattt ctgtatgtct 540
ctgaccagac acccatcaac agtattattt tctcccatga agacggtagc cgactggcgg 600
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| | | | | | | |
|------------|--------------|-------------|-------------|------------|------------|------|
| tggagcatct | ggtcgcattg | ggtcaccaggc | aaatcgcgct | gttagcgggc | ccattaagtt | 660 |
| ctgtctcggt | gcgtctcggt | ctggctggct | ggcataaata | tctcactcgc | aatcaaattc | 720 |
| agccgatagc | ggaacggaa | ggcgactgga | gtgccatgtc | cggtttcaa | caaaccatgc | 780 |
| aaatgctgaa | tgagggcatc | gttcccactg | cgatgctggt | tgccaaacgt | cagatggcgc | 840 |
| tggcgcaat | gcfgccatt | accgagtccg | ggctgcgcgt | tggtgccgat | atctcggtag | 900 |
| tgggatacga | cgataccgaa | gacagctcat | gttatatccc | gccgttaacc | accatcaaac | 960 |
| aggattttcg | cctgctgggg | caaaccagcg | tggaccgctt | gctgcaactc | tctcagggcc | 1020 |
| aggcggtaaa | gggcaatcag | ctgttgcgg | tctcactggt | aaaaagaaaa | accaccctgg | 1080 |
| cgcggccat | gcaaaaccggcc | tctcccccgcg | cgttggccga | ttcattaatg | cagctggcac | 1140 |
| gacaggtttc | ccgactggaa | agcggacagt | aaggtaaccat | aggatccagg | cacagga | 1197 |

<210> 100

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Modulators of TALL-1

<220>

<221> misc_feature

<222> (1, 2, 3, 13)..(14)

<223> Xaa (Pos1,2,3,13,14) are each independently absent or amino acid residues;

<220>

<221> misc_feature

<222> (6)..(6)

<223> Xaa (Pos6) is an amino acid residue; Xaa (Pos9) is a basic or hydrophobic residue;

<220>

<221> misc_feature

<222> (12)..(12)

<223> Xaa (Pos12) is a neutral hydrophobic residue.

<400> 100

| | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Xaa | Xaa | Cys | Asp | Xaa | Leu | Thr | Xaa | Xaa | Cys | Xaa | Xaa | Xaa |
| 1 | | | | | 5 | | | | 10 | | | | |

<210> 101

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Modulators of TALL-1

<220>

<221> misc_feature

<222> (1, 2, 3, 12 and)..(13)

<223> Xaa (Pos1,2,3,12,13) are each independently absent or amino acid

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residues;

<220>
<221> misc_feature
<222> (5 and) .. (8)
<223> Xaa (Pos5,8) is a neutral hydrophobic residue; Xaa (Pos10) is an acidic residue;

<220>
<221> misc_feature
<222> (14) .. (14)
<223> Xaa (Pos14) is absent or is an amino acid residue.

<400> 101

Xaa Xaa Xaa Cys Xaa Pro Phe Xaa Trp Xaa Cys Xaa Xaa Xaa
1 5 10

<210> 102
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 12, 13 and) .. (14)
<223> Xaa (Pos1,2,3,12,13,14) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (6 and) .. (7)
<223> Xaa (Pos6,7) is a hydrophobic residue;

<220>
<221> misc_feature
<222> (10) .. (10)
<223> Xaa (Pos10) is an acidic or polar hydrophobic residue.

<400> 102

Xaa Xaa Xaa Xaa Trp Xaa Xaa Trp Gly Xaa Xaa Xaa Xaa
1 5 10

<210> 103
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1) .. (1)
<223> Xaa (Pos1) is absent or is an amino acid residue;

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```
<220>
<221> misc_feature
<222> (2 and)..(14)
<223> Xaa (Pos2,14) is a neutral hydrophobic residue;

<220>
<221> misc_feature
<222> (3 and)..(10)
<223> Xaa (Pos3,10) is an amino acid residue;

<220>
<221> misc_feature
<222> (5, 6, 7, 8, 12 and)..(13)
<223> Xaa (Pos5,6,7,8,12,13) are each independently amino acid residues
;

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa (Pos9) is an acidic residue.

<400> 103

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1 5 10

<210> 104
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 12, 13, 16, 17 and)..(18)
<223> Xaa (Pos1,2,12,13,16,17,18) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa (Pos3) is an acidic or amide residue;

<220>
<221> misc_feature
<222> (5 and)..(8)
<223> Xaa (Pos5,8) is an amino acid residue;

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa (Pos6) is an aromatic residue;

<220>
<221> misc_feature
<222> (11)..(11)
```

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<223> Xaa (Pos11) is a basic residue;

<220>

<221> misc_feature

<222> (14)..(14)

<223> Xaa (Pos14) is a neutral hydrophobic residue.

<400> 104

Xaa Xaa Xaa Cys Xaa Xaa Asp Xaa Leu Thr Xaa Xaa Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa

<210> 105

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Modulator of TALL-1

<220>

<221> misc_feature

<222> (1, 2 and)..(3)

<223> Xaa (Pos1,2,3) are each independently absent or amino acid residues;

<220>

<221> misc_feature

<222> (5, 7, 14 and)..(16)

<223> Xaa (Pos5,7,14,16) is an amino acid residue;

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa (Pos10) is a basic residue;

<220>

<221> misc_feature

<222> (11 and)..(12)

<223> Xaa (Pos11,12) are each independently amino acid residues;

<220>

<221> misc_feature

<222> (13 and)..(17)

<223> Xaa (Pos13,17) is a neutral hydrophobic residue;

<220>

<221> misc_feature

<222> (18)..(18)

<223> Xaa (Pos18) is an amino acid residue or is absent.

<400> 105

Xaa Xaa Xaa Cys Xaa Asp Xaa Leu Thr Xaa Xaa Xaa Xaa Cys Xaa

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1

5

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10

15

Xaa Xaa

<210> 106
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 16, 17 and)...(18)
<223> Xaa (Pos1,2,3,16,17,18) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 10, 13 and)...(14)
<223> Xaa (Pos5,6,7,10,13,14) are each independently amino acid residues.

<400> 106

Xaa Xaa Xaa Cys Xaa Xaa Xaa Trp Asp Xaa Leu Thr Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa

<210> 107
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1,2,3,15,16,17)...(18)
<223> Xaa (Pos1,2,3,15,16,17,18) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 9 and)...(13)
<223> Xaa (Pos 5,6,7,9 13) are each independently amino acid residues;

<220>
<221> misc_feature
<222> (11)...(11)
<223> Xaa (Pos 11) is T or I; and

<400> 107

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Xaa Xaa Xaa Cys Xaa Xaa Xaa Asp Xaa Leu Xaa Lys Xaa Cys Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 108
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (2)..(2)
<223> X at (Pos 2) is an amino acid residue

<220>
<221> misc_feature
<222> (4)..(4)
<223> X at (Pos 4) is threonyl or isoleucyl

<400> 108

Asp Xaa Leu Xaa
1

<210> 109
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2 and)..(3)
<223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
e of X1, X2, and X3 preferred to be C when one of X12,
X13, an
d X14 is C);

<220>
<221> misc_feature
<222> (5)..(5)
<223> X at (Pos 5) is W, Y, or F (W preferred);

<220>
<221> misc_feature
<222> (7)..(7)
<223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
<221> misc_feature
<222> (9)..(9)
<223> X at (Pos 9) is T or I (T preferred);

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<220>
 <221> misc_feature
 <222> (10)..(10)
 <223> X at (Pos 10) is K, R, or H (K preferred).

<220>
 <221> misc_feature
 <222> (12)..(12)
 <223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic residue (W, C, or R preferred);

<220>
 <221> misc_feature
 <222> (13)..(13)
 <223> X at (Post 13) is C, a neutral hydrophobic residue or is absent (V preferred);

<220>
 <221> misc_feature
 <222> (14)..(14)
 <223> X at (Pos 14) is any amino acid residue or is absent.

<400> 109

Xaa Xaa Xaa Lys Xaa Asp Xaa Leu Xaa Xaa Gln Xaa Xaa Xaa
 1 5 10

<210> 110
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Modulator of TALL-1

<400> 110

Pro Phe Pro Trp Glu
 1 5

<210> 111
 <211> 248
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 111

Met Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala Gly
 1 5 10 15

Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 35 40 45

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Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 112

<211> 248

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 112

Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
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20

25

30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
 245

<210> 113
 <211> 248
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 113

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Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly
1 5 10 15

Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 114
<211> 252
<212> PRT

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<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 114

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Ser | Arg | Cys | Lys | Tyr | Lys | Trp | Asp | Val | Leu | Thr | Lys | Gln | Cys |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | His | His | Gly | Gly | Gly | Gly | Val | Asp | Lys | Thr | His | Thr | Cys | Pro |
| | | | 20 | | | 25 | | | | | 30 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Cys | Pro | Ala | Pro | Glu | Leu | Leu | Gly | Gly | Pro | Ser | Val | Phe | Leu | Phe |
| | | | | | 35 | | | 40 | | | 45 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Pro | Lys | Pro | Lys | Asp | Thr | Leu | Met | Ile | Ser | Arg | Thr | Pro | Glu | Val |
| | | | | | 50 | | | 55 | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Cys | Val | Val | Val | Asp | Val | Ser | His | Glu | Asp | Pro | Glu | Val | Lys | Phe |
| | | | | | 65 | | | 70 | | 75 | | 80 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Trp | Tyr | Val | Asp | Gly | Val | Glu | Val | His | Asn | Ala | Lys | Thr | Lys | Pro |
| | | | | | 85 | | | 90 | | | | 95 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Glu | Gln | Tyr | Asn | Ser | Thr | Tyr | Arg | Val | Val | Ser | Val | Leu | Thr |
| | | | | | 100 | | | 105 | | | | 110 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Leu | His | Gln | Asp | Trp | Leu | Asn | Gly | Lys | Glu | Tyr | Lys | Cys | Lys | Val |
| | | | | | 115 | | | 120 | | | 125 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asn | Lys | Ala | Leu | Pro | Ala | Pro | Ile | Glu | Lys | Thr | Ile | Ser | Lys | Ala |
| | | | | | 130 | | | 135 | | | 140 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Gln | Pro | Arg | Glu | Pro | Gln | Val | Tyr | Thr | Leu | Pro | Pro | Ser | Arg |
| | | | | | 145 | | | 150 | | 155 | | 160 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Glu | Leu | Thr | Lys | Asn | Gln | Val | Ser | Leu | Thr | Cys | Leu | Val | Lys | Gly |
| | | | | | 165 | | | 170 | | | 175 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Tyr | Pro | Ser | Asp | Ile | Ala | Val | Glu | Trp | Glu | Ser | Asn | Gly | Gln | Pro |
| | | | | | 180 | | | 185 | | | 190 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asn | Asn | Tyr | Lys | Thr | Thr | Pro | Pro | Val | Leu | Asp | Ser | Asp | Gly | Ser |
| | | | | | 195 | | | 200 | | | 205 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Phe | Leu | Tyr | Ser | Lys | Leu | Thr | Val | Asp | Lys | Ser | Arg | Trp | Gln | Gln |
| | | | | | 210 | | | 215 | | | 220 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Asn | Val | Phe | Ser | Cys | Ser | Val | Met | His | Glu | Ala | Leu | His | Asn | His |
| | | | | | 225 | | | 230 | | 235 | | 240 | | | |

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Thr | Gln | Lys | Ser | Leu | Ser | Leu | Ser | Pro | Gly | Lys |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

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250

<210> 115
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies
 <400> 115

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
 1 5 10 15

Asp Pro Leu Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

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Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 116
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 116

Met Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
 1 5 10 15

Thr Ser Ser Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
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 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 117
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 117

Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys
 1 5 10 15

Ser Asn Leu Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

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Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 118

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 118

Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys
 1 5 10 15

Gln Phe Asn Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
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145

150

155

160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 119

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 119

Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
 1 5 10 15

His Gly Leu Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

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Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 120

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 120

Met Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys
1 5 10 15

Pro Ser Pro Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
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100

105

110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 121
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> TALL-1 inhibitory peptibodies

<400> 121

Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys
 1 5 10 15

Glu Phe Phe Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
 20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

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Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 122
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 122

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
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50

55

60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 245 250

<210> 123

<211> 293

<212> PRT

<213> Artificial Sequence

<220>

<223> TALL-1 inhibitory peptibodies

<400> 123

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
 1 5 10 15

Asp Pro Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
 20 25 30

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Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp
 35 40 45

Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly
 50 55 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 130 135 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 225 230 235 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 245 250 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 260 265 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 275 280 285

Leu Ser Pro Gly Lys
 290

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<210> 124
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 124

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
20 25 30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Phe His Asp Cys Lys Trp
35 40 45

Asp Leu Leu Thr Lys Gln Trp Val Cys His Gly Leu Gly Gly Gly
50 55 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
130 135 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
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225

230

235

240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
245 250 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
260 265 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
275 280 285

Leu Ser Pro Gly Lys
290

<210> 125

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus Sequence

<220>

<221> misc_feature

<222> (1, 2 and) .. (3)

<223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with one of X1, X2, X3 preferred to be C when one of X12, X13, and X14 is C);

<220>

<221> misc_feature

<222> (7) .. (7)

<223> X at (Pos 7) is an amino acid residue (L preferred);

<220>

<221> misc_feature

<222> (9) .. (9)

<223> X at (Pos 9) is T or I (T preferred);

<220>

<221> misc_feature

<222> (12) .. (12)

<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic residue (W, C, or R preferred);

<220>

<221> misc_feature

<222> (13) .. (13)

<223> X at (Pos 13) is C, a neutral hydrophobic residue or is absent (V

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preferred);

<220>
<221> misc_feature
<222> (14)..(14)
<223> X at (Pos 14) is any amino acid residue or is absent.

<400> 125

Xaa Xaa Xaa Lys Trp Asp Xaa Leu Xaa Lys Gln Xaa Xaa Xaa
1 5 10

<210> 126
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 126

Tyr Lys Gly Arg Gln Met Trp Asp Ile Leu Thr Arg Ser Trp Val Val
1 5 10 15

Ser Leu

<210> 127
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 127

Gln Asp Val Gly Leu Trp Trp Asp Ile Leu Thr Arg Ala Trp Met Pro
1 5 10 15

Asn Ile

<210> 128
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 128

Gln Asn Ala Gln Arg Val Trp Asp Leu Leu Ile Arg Thr Trp Val Tyr
1 5 10 15

Pro Gln

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<210> 129
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 129

Gly Trp Asn Glu Ala Trp Trp Asp Glu Leu Thr Lys Ile Trp Val Leu
1 5 10 15

Glu Gln

<210> 130
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 130

Arg Ile Thr Cys Asp Thr Trp Asp Ser Leu Ile Lys Lys Cys Val Pro
1 5 10 15

Gln Ser

<210> 131
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 131

Gly Ala Ile Met Gln Phe Trp Asp Ser Leu Thr Lys Thr Trp Leu Arg
1 5 10 15

Gln Ser

<210> 132
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 132

Trp Leu His Ser Gly Trp Trp Asp Pro Leu Thr Lys His Trp Leu Gln
1 5 10 15

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Lys Val

<210> 133
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 133

Ser Glu Trp Phe Phe Trp Phe Asp Pro Leu Thr Arg Ala Gln Leu Lys
1 5 10 15

Phe Arg

<210> 134
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 134

Gly Val Trp Phe Trp Trp Phe Asp Pro Leu Thr Lys Gln Trp Thr Gln
1 5 10 15

Ala Gly

<210> 135
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 135

Met Gln Cys Lys Gly Tyr Tyr Asp Ile Leu Thr Lys Trp Cys Val Thr
1 5 10 15

Asn Gly

<210> 136
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 136

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Leu Trp Ser Lys Glu Val Trp Asp Ile Leu Thr Lys Ser Trp Val Ser
1 5 10 15

Gln Ala

<210> 137
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 137

Lys Ala Ala Gly Trp Trp Phe Asp Trp Leu Thr Lys Val Trp Val Pro
1 5 10 15

Ala Pro

<210> 138
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 138

Ala Tyr Gln Thr Trp Phe Trp Asp Ser Leu Thr Arg Leu Trp Leu Ser
1 5 10 15

Thr Thr

<210> 139
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 139

Ser Gly Gln His Phe Trp Trp Asp Leu Leu Thr Arg Ser Trp Thr Pro
1 5 10 15

Ser Thr

<210> 140
<211> 18
<212> PRT
<213> Artificial Sequence

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<220>
<223> Preferred TALL-1 modulating domains
<400> 140

Leu Gly Val Gly Gln Lys Trp Asp Pro Leu Thr Lys Gln Trp Val Ser
1 5 10 15

Arg Gly

<210> 141
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 141

Val Gly Lys Met Cys Gln Trp Asp Pro Leu Ile Lys Arg Thr Val Cys
1 5 10 15

Val Gly

<210> 142
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 142

Cys Arg Gln Gly Ala Lys Phe Asp Leu Leu Thr Lys Gln Cys Leu Leu
1 5 10 15

Gly Arg

<210> 143
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 143

Gly Gln Ala Ile Arg His Trp Asp Val Leu Thr Lys Gln Trp Val Asp
1 5 10 15

Ser Gln

<210> 144

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<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 144

Arg Gly Pro Cys Gly Ser Trp Asp Leu Leu Thr Lys His Cys Leu Asp
1 5 10 15

Ser Gln

<210> 145
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 145

Trp Gln Trp Lys Gln Gln Trp Asp Leu Leu Thr Lys Gln Met Val Trp
1 5 10 15

Val Gly

<210> 146
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 146

Pro Ile Thr Ile Cys Arg Lys Asp Leu Leu Thr Lys Gln Val Val Cys
1 5 10 15

Leu Asp

<210> 147
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 147

Lys Thr Cys Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln
1 5 10 15

Gln Ala

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<210> 148
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 148

Lys Cys Leu Lys Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Thr
1 5 10 15

Glu Val

<210> 149
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 149

Arg Cys Trp Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile His
1 5 10 15

Pro Trp

<210> 150
<211> 18
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<220>
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<400> 150

Asn Arg Asp Met Arg Lys Trp Asp Pro Leu Ile Lys Gln Trp Ile Val
1 5 10 15

Arg Pro

<210> 151
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 151

Gln Ala Ala Ala Ala Thr Trp Asp Leu Leu Thr Lys Gln Trp Leu Val
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10

15

Pro Pro

<210> 152
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 152

Pro Glu Gly Gly Pro Lys Trp Asp Pro Leu Thr Lys Gln Phe Leu Pro
1 5 10 15

Pro Val

<210> 153
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 153

Gln Thr Pro Gln Lys Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Thr
1 5 10 15

Arg Asn

<210> 154
<211> 18
<212> PRT
<213> Artificial Sequence

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<400> 154

Ile Gly Ser Pro Cys Lys Trp Asp Leu Leu Thr Lys Gln Met Ile Cys
1 5 10 15

Gln Thr

<210> 155
<211> 18
<212> PRT
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<220>
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<400> 155

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Thr | Ala | Ala | Gly | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Ile | Gln |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Glu Lys

<210> 156

<211> 18

<212> PRT

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<400> 156

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Gln | Cys | Met | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Cys | Leu | Gln |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Gly Trp

<210> 157

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 157

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Trp | Gly | Thr | Trp | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Tyr | Leu | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Pro Gln

<210> 158

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 158

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Trp | Trp | Glu | Met | Lys | Trp | Asp | Leu | Leu | Thr | Lys | Gln | Trp | Tyr | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Pro Gln

<210> 159

<211> 18

<212> PRT

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<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 159

Thr Ala Gln Val Ser Lys Trp Asp Leu Leu Thr Lys Gln Trp Leu Pro
1 5 10 15

Leu Ala

<210> 160

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 160

Gln Leu Trp Gly Thr Lys Trp Asp Leu Leu Thr Lys Gln Tyr Ile Gln
1 5 10 15

Ile Met

<210> 161

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 161

Trp Ala Thr Ser Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Asn Met

<210> 162

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred TALL-1 modulating domains

<400> 162

Gln Arg Gln Cys Ala Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Leu
1 5 10 15

Phe Tyr

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<210> 163
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 163

Lys Thr Thr Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Arg Ile Cys
1 5 10 15

Gln Val

<210> 164
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 164

Leu Leu Cys Gln Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Lys
1 5 10 15

Leu Arg

<210> 165
<211> 18
<212> PRT
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<220>
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<400> 165

Leu Met Trp Phe Trp Lys Trp Asp Leu Leu Thr Lys Gln Leu Val Pro
1 5 10 15

Thr Phe

<210> 166
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

<400> 166

Gln Thr Trp Ala Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gly
1 5 10 15

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Pro Met

<210> 167
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 167

Asn Lys Glu Leu Leu Lys Trp Asp Leu Leu Thr Lys Gln Cys Arg Gly
1 5 10 15

Arg Ser

<210> 168
<211> 18
<212> PRT
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<220>
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<400> 168

Gly Gln Lys Asp Leu Lys Trp Asp Leu Leu Thr Lys Gln Tyr Val Arg
1 5 10 15

Gln Ser

<210> 169
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 169

Pro Lys Pro Cys Gln Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gly
1 5 10 15

Ser Val

<210> 170
<211> 18
<212> PRT
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<220>
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<400> 170

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Gly Gln Ile Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gln
1 5 10 15

Thr Arg

<210> 171
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

<400> 171

Val Trp Leu Asp Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile His
1 5 10 15

Pro Gln

<210> 172
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 172

Gln Glu Trp Glu Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Gly Trp
1 5 10 15

Leu Arg

<210> 173
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

<400> 173

His Trp Asp Ser Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Val
1 5 10 15

Gln Ala

<210> 174
<211> 18
<212> PRT
<213> Artificial Sequence

A-743 PCT.ST25.txt

<220>
<223> Preferred TALL-1 modulating domains
<400> 174

Thr Arg Pro Leu Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Leu Arg
1 5 10 15

Val Gly

<210> 175
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 175

Ser Asp Gln Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Trp
1 5 10 15

Asp Val

<210> 176
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains
<400> 176

Gln Gln Thr Phe Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Arg
1 5 10 15

Arg His

<210> 177
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 177

Gln Gly Glu Cys Arg Lys Trp Asp Leu Leu Thr Lys Gln Cys Phe Pro
1 5 10 15

Gly Gln

<210> 178

A-743 PCT.ST25.txt

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 178

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Ile Lys Met Cys Leu Gly
1 5 10 15

Pro Ser

<210> 179
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 179

Gln Leu Asp Gly Cys Lys Trp Asp Leu Leu Thr Lys Gln Lys Val Cys
1 5 10 15

Ile Pro

<210> 180
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 180

His Gly Tyr Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Ser
1 5 10 15

Ser Glu

<210> 181
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

<400> 181

His Gln Gly Gln Cys Gly Trp Asp Leu Leu Thr Arg Ile Tyr Leu Pro
1 5 10 15

Cys His

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<210> 182
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 182

Leu His Lys Ala Cys Lys Trp Asp Leu Leu Thr Lys Gln Cys Trp Pro
1 5 10 15

Met Gln

<210> 183
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 183

Gly Pro Pro Gly Ser Val Trp Asp Leu Leu Thr Lys Ile Trp Ile Gln
1 5 10 15

Thr Gly

<210> 184
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 184

Ile Thr Gln Asp Trp Arg Phe Asp Thr Leu Thr Arg Leu Trp Leu Pro
1 5 10 15

Leu Arg

<210> 185
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 185

Gln Gly Gly Phe Ala Ala Trp Asp Val Leu Thr Lys Met Trp Ile Thr
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10

15

Val Pro

<210> 186
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 186

Gly His Gly Thr Pro Trp Trp Asp Ala Leu Thr Arg Ile Trp Ile Leu
1 5 10 15

Gly Val

<210> 187
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 187

Val Trp Pro Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Phe Val Phe
1 5 10 15

Gln Asp

<210> 188
<211> 19
<212> PRT
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<220>
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<400> 188

Trp Gln Gln Trp Ser Trp Lys Trp Asp Leu Leu Thr Arg Gln Tyr Ile
1 5 10 15

Ser Ser Ser

<210> 189
<211> 882
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<220>
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 atgcttccag gctgcaagtg ggatcttctt attaagcaat gggtatgcga tccacttggaa 60
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 catatgctgc cgggttgtaa atgggacctg ctgatcaaac agtgggtttg tgacccgctg 180
 ggtggaggcg gtggggtcga caaaactcac acatgtccac cttgtccagc tccggaactc 240
 ctggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 300
 cggacccctg aggtcacatg cgtgggtgg gacgtgagcc acgaagaccc tgaggtcaag 360
 ttcaactggt acgtggacgg cgtggagggtg cataatgcca agacaaagcc gcgggaggag 420
 cagtacaaca gcacgtaccc tgggtcagc gtcctcaccc tcctgcacca ggactggctg 480
 aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 540
 accatctcca aagccaaagg gcagccccga gaaccacagg tggactccct gccccatcc 600
 cgggatgagc tgaccaagaa ccaggtcagc ctgacccgtcc tggtcaaagg cttctatccc 660
 agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 720
 cctccctgtgc tggactccga cggctccttc ttccctctaca gcaagctcac cgtggacaag 780
 agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcattgaggc tctgcacaac 840
 cactacacgc agaagagcct ctccctgtct ccgggtaaat aa 882

<210> 190

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred linker

<400> 190

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Gly | Ser | Ala | Thr | Gly | Gly | Ser | Gly | Ser | Thr | Ala | Ser | Ser | Gly |
| 1 | | | | | | | | | | | | | | | 15 |

| | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Ser | Ala | Thr | Gly | Met |
| | | | | | | 20 |

<210> 191

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Preferred linker

<400> 191

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Gly | Ser | Ala | Thr | Gly | Gly | Ser | Gly | Ser | Thr | Ala | Ser | Ser | Gly |
| 1 | | | | | | | | | | | | | | | 15 |

| | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Ser | Ala | Thr | Gly | Ser |
| | | | | | | 20 |

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Ser Gly Ser Ala Thr Xaa Xaa Gly Ser Gly Ser Ala Thr Gly Gly Ser
20 25 30

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Xaa Xaa
35 40 45

<210> 195
<211> 38
<212> PRT
<213> Human

<400> 195

Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Val Pro
1 5 10 15

Thr Pro Cys Val Pro Thr Glu Cys Tyr Asp Leu Leu Val Arg Lys Cys
20 25 30

Val Asp Cys Arg Leu Leu
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<210> 196
<211> 41
<212> PRT
<213> Human

<400> 196

Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg
1 5 10 15

Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu
20 25 30

Arg Asp Cys Ile Ser Cys Ala Ser Ile
35 40

<210> 197
<211> 42
<212> PRT
<213> Human

<400> 197

Phe Val Ser Pro Ser Gln Glu Ile Arg Gly Arg Phe Arg Arg Met Leu
1 5 10 15

Gln Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser Leu Leu
20 25 30

His Ala Cys Ile Pro Cys Gln Leu Arg Cys
35 40